deficiency at 15 days. The cases that occurred within 10 days were probably either not rubella or were infected from a source other than the first case recorded in the family. The exclusion of these cases would lower the

FIG. 3.—Distribution of serial intervals between primary and all subsequent cases of rubella in the family.

secondary attack rates. In women aged 17–44 years, for example, the rate for secondary cases with onset 11–28 days after the primary was 3.3% ; in women with no definite past history of the disease it was 4.8%.

Discussion

The diagnosis of rubella is difficult to make with certainty, especially when there is only one case in the family. As diseases which may be mistaken for rubella are probably less likely to cause secondary cases, particularly in adults, the attack rates in this survey may tend to be lower than they should be. The same problems of diagnosis apply equally, however, to attack rates after gamma-globulin, and to all observations on the risk to the foetus of maternal rubella. On the whole we feel that the rates shown are probably reasonably close to the truth.

The much higher attack rates in adult women than in men was also noted by Hillenbrand (1956) in his description of an epidemic in the Falkland Islands. The same tendency is seen in other communicable diseases, presumably owing to the closer contact of children with their mothers than their fathers. The difference in rubella seems particularly large, so possibly there is some other contributing factor.

The apparent resistance to infection of infants in the first six months of life implies, among other possible factors, the acquisition of maternal antibody from the mother as in measles. This alone would justify some hope of protection from gamma-globulin. Compared with measles the secondary attack rates in childhood are much lower in rubella, but the resistance of adults to infection in both diseases is similar. A high incidence of inapparent infection in rubella seems the most likely explanation of these findings.

From a practical viewpoint it may be useful for doctors to know that non-pregnant adult women have about a 4% chance of contracting rubella when exposed to a case in their household. The risk is slightly higher if the woman has no past history of the disease and much lower if she has. Assuming the risk attributable to rubella of death or major defect in the foetus to be 25% in women who contract infection in the first 12 weeks of pregnancy (Manson *et al.*, 1960), the risk of foetal damage for women exposed to infection in the family is not less than 1% over the whole period and is higher in the earlier weeks. This estimate of the hazard does not take into account lesser degrees of deafness attributable to rubella and emphasizes the need for an effective means of immunization.

Summary

Between June, 1957, and the end of 1960 510 cases of rubella, the first to occur in 506 families, were notified by general practitioners. Records were obtained of all members of each patient's household and whether or not they developed the disease.

None of 14 contacts under 6 months of age were attacked, and very few at any age with a past history of rubella.

Over a third of the contacts aged less than 10 years were attacked and rates then fell with advancing age.

The attack rate in women of child-bearing age (17–44 years) was 3.7%, but it was 1.0% in those said to have had rubella previously and 5.5% in those with no past history. The rate for adult men was about one-tenth that for women.

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RUBELLA IN THE NEWBORN

BY

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Although rubella was first described in Germany by De Bergen in 1752 and by Orlow in 1758 it was considered a relatively unimportant disease in childhood until 1941, when Gregg, in Australia, made the clinical observation that maternal rubella in early pregnancy was followed by congenital cataract and malformation of the heart. Since that time numerous other congenital defects as well as complications of pregnancy have been documented and the events which follow maternal rubella have become known as the rubella syndrome.

Hill *et al.* (1958) and Manson *et al.* (1960) carried out prospective studies of the effect on pregnancy of a considerable number of viral infections affecting the mother. Of these, only maternal rubella was considered to be a major problem. Liggins and Phillips (1963) conducted a prospective survey of maternal rubella in New Zealand. Campbell (1961) and Skinner (1961) have reviewed the problem in detail.

In this paper are reported four cases of a hitherto only briefly recorded entity, rubella in the newborn ; it is suggested that one of these cases illustrates a fundamental question on the rubella problem.

The Four Cases

Two of the cases occurred in my practice in August, 1962, during an epidemic of rubella in this area. The other two occurred in Dr. W. J. Wren's practice in Lowestoft during a similar epidemic in June, 1962. Lowestoft is 125 miles (200 km.) by air from Nottingham. Wren (1962) has referred briefly to these cases. I am grateful to him for subsequently supplying full details of his two cases, Babies B 1 and B 2, and for his permission to include them in this paper.

The first four weeks of life is taken as a definition of the newborn period. In all four babies, aged 12, 24, 25, and 26 days on the occurrence of the rash (see Table), the course of the disease was remarkably similar.

Details of Cases

Baby	Age (Days)	History of Rubella in Mother	Present Age of Mother	Feeding	Medication Prior to Onset of Rash		Place of Birth
					Mother while Breast-feeding	Baby	
C	12	Definite, aged 2 years	31	Breast-fed for 10 days then Ostermilk Fully breast-fed	None	Gripe water	Hospital
B 1	24	Suspected, aged 8 years	22	Fully breast-fed	„	None	Home
W	25	No known history	26	Breast-fed for 10 days Then C. and G.	“Seno-kot”	Gripe water	„
B 2	26	Definite, aged 6 years	22	Breast-fed for 2 weeks then N.D.M.	None	None	„

The prodromal symptoms were negligible, in that the mothers noted in retrospect that the babies had been mildly fretful and off their feeds on the day before the occurrence of the rash. When seen next day the babies did not appear at all ill, but each had a generalized pink maculopapular rash of the face, neck, trunk, and limbs—if anything, this was more marked on the trunk. The individual lesions were more macular than papular, each was distinct though closely packed together, and each measured approximately 0.5–1.5 mm. across. In no case was the baby pyrexial and in all four cases enlarged and discrete posterior cervical and occipital lymph nodes were noted; in the 12-day-old infant (Baby C) these were present but not as numerous as in the others. In all cases the rash was confluent within 24 hours, the papular element was by then more apparent, and the rash closely resembled that of scarlet fever. In Babies C and W the axillary temperature at that time was 98.8 and 98.6° F. (37.1 and 37° C.), respectively. By the next day the rash was fading, all babies were afebrile, and all were feeding and sleeping well. At no time had any of them been more than mildly fretful. By the fourth day there was no sign of the rash in any of them, and by the seventh day the lymph nodes were no longer palpable in Babies B 1 and B 2. At no time was any generalized lymphadenopathy or hepatosplenomegaly noted. In none was there any sign of infection of the upper respiratory tract or of meningeal involvement. Koplik spots were not noted in any of the cases. None of the infants required any form of therapy.

Throat swabs were taken on the first day from Babies C and W, not because there was any throat involvement, but to serve as a means of differential diagnosis. In neither case was β -haemolytic streptococcus isolated on culture. Colour photographs were taken of these two babies on the day of the appearance of the rash.

The natural incubation period of rubella is accepted as being between 14 and 21 days. This is well illustrated in noting the probable course of the incubation period in Baby C.

Baby C.—On August 10, 1962, a boy aged 6½ years was diagnosed by his family doctor (Dr. K. D. Murison, of Beeston) as suffering from classical rubella. For the few days up to the appearance of the rash he had been virtually living in the house of a neighbour who was almost at term, during her tenth pregnancy. For the next few days he was visited on a number of occasions at his own home by that neighbour. On August

18 the contact, a woman aged 31, who was thought to have had rubella at the age of 2 years, at the same time as had her sister, was admitted in labour to hospital, where on the same day she gave spontaneous birth to a healthy male child weighing 7 lb. 7½ oz. (3,390 g.). She and the baby remained in hospital until their discharge home on August 27. On August 30 the baby was first seen by me on account of the development of the generalized rash previously referred to. It was learned later that on the same day as Baby C developed his rash, the sister, aged 5 years, of the original case was seen at home and diagnosed as suffering from classical rubella (Dr. A. H. Brittain, of Beeston). Neither during the pregnancy nor after the baby's illness did the mother develop any rash, nor did she appear in the least ill. She was under observation for the next three weeks but developed no palpably tender posterior cervical, posterior auricular, or occipital lymph nodes.

It is accepted (Campbell, 1961) that the virus of rubella circulates in the maternal blood during and for a short time after the incubation period and passes through the chorionepithelium to the blood-stream of the foetus. It is postulated that this happened in the case of Baby C and that at his birth he was still incubating the disease, which did not become manifest until the natural completion of the incubation period.

Differential Diagnosis

If we accept that the disease described was the same in each baby, its close resemblance to rubella is apparent. There was the lack of prodromal and constitutional signs, including pyrexia. The change from an initial maculopapular eruption to one of a scarlatiniform appearance on the second day was characteristic. Posterior cervical and occipital glands were palpable, and there was no generalized lymphadenopathy. Each illness occurred during a country-wide epidemic of rubella. Two of the cases were 125 miles (200 km.) distant from the other two and occurred two months later than them. Although the only known contact was indirect in one case (Baby C) the other infants were born at home, and relatives, neighbours, and friends had easy access to them. There were no other similar cases in the family circles involved, many of those at risk already having had rubella. This is well illustrated in the case of Baby C. Five people lived in the house, all of whom had had rubella in the past, and none of these developed a rash, as would have been expected had the illness been due to one of the enteroviruses (Sanford and Sulkin, 1959).

From the Table it can be seen that there was no similarity in the feeding of any of the babies, nor can medication either direct or through the mother's milk be blamed. Teething, if it ever does cause exanthema, could hardly be blamed.

During a comprehensive review of the literature I have been unable to compare or contrast the course of the disease in the four babies with any exanthematous illness other than rubella. The clinical diagnosis of rubella was discussed by McLorinan (1950) and reviewed by Stokes (1960). Robinson *et al.* (1958) have drawn up a most detailed table comparing the main clinical features of epidemic short-term fevers which may present with a maculopapular rash.

Discussion

No reported cases of rubella occurring in the newborn could be found other than those of Wren (1962), two of whose cases have been more fully reported above.

Readett and McGibbon (1961) reported *neonatal vari-*

cella in two babies who were in contact with the disease from the first day of life.

A number of cases of prenatal viral infections of the foetus have been reported often with a history of contact but with no obvious infection in the mother. Wielenga *et al.* (1961) reported the case of widespread and fatal prenatal infection with vaccinia virus in a 27½-weeks-old foetus whose mother had not previously been vaccinated, but whose 11-months-old son had been vaccinated when she was 18 weeks pregnant. The mother had shown no sign of skin eruption. Hubbard (1878) reported a case of neonatal varicella in a 2-day-old child who developed the typical skin eruption. There was no known exposure—that is, the mother did not have the disease—and there were no known contacts. Schick (1949) reported a number of case histories of foetal infection by variola in mothers showing no evidence of the disease, in view either of previous infection or of vaccination, but having been exposed to the disease in pregnancy.

Schick compares the lack of immunity in the foetus to variola as being similar to a lack of immunity in the foetus to rubella, whether or not the mother had previously had rubella. He concludes that the danger of infecting the foetus is less great when the mother has had rubella only one or two years before pregnancy, rather than many years before, because circulating antibodies from a not-distant active disease are more likely to be present.

The rarity of rubella and allied viral infections in the newborn might well, however, suggest an unusual degree of susceptibility of the host to viral infection, rather than a failure of antibodies to neutralize.

I believe that the case of Baby C, prenatally incubating rubella, represents the "missing link" between theory and evidence that previously suspected maternal subclinical rubella during the first trimester of pregnancy could be responsible for cases of subsequent rubella syndrome.

Warkany (1957) reported the case of a child with cataract and congenital heart disease born to a mother who was unaware of any illness during pregnancy, but two of her older children had had rubella when she was in the second month of her pregnancy.

A somewhat similar case is described by Malmberg *et al.* (1957). A mother exposed to rubella infection during the third month of pregnancy was given immune globulin prophylactically. She gave birth at term to a child with evidence of embryopathy (organic heart disease and cataract) without having had any signs or symptoms of rubella herself. The authors explain the asymptomatic illness in the mother as being due to the injection of immune globulin, which was given too late in the incubation period (sixth to eighth day) to protect the foetus. No mention is made as to whether or not the mother was thought to have previously had rubella and if so at what age.

That this question is significant is shown by the observations of Lundström (1952), who found that, in occasional cases where the mother has become immune after having had rubella earlier in her life, it is probable that the foetus can be infected and injured if the mother is again exposed to rubella infection. In a group of mothers who had been exposed to rubella, but who were probably immune, Lundström found that the number of children born with malformations was significantly greater than in a control group of unexposed but immune mothers. Lundström and Krugman (1956) pointed out that allowance must be made for the possibility of a few mothers in the above

group not having had rubella at an earlier age but some other disease, and hence had not been immune but had as a result of the exposure contracted rubella without a rash.

Coffey and Jessop (1959) supported the impression that a history of rubella in the mother is not always sufficient to protect the foetus. They reported a prospective study of 75 cases in Dublin and noted that women who were exposed to, but did not exhibit signs of, rubella produced offspring with anomalies at a rate that was two and a half times as great as that seen in the general population.

Reports on rubella as a cause of foetal abnormality stress that there is no relationship between the severity of the maternal infection and the nature of the defect in the child. This led Krugman *et al.* (1953) in their studies on rubella immunization to raise what they called "a very important practical question"—this was posed by the significant finding that the same causative agent that produced typical rubella with rash also produced rubella without rash, the first direct proof of such a possibility. The question thus raised was, "Would an inapparent rubella infection acquired during the first trimester of pregnancy have the same deleterious effect on the foetus as that which is associated with the typical infection?" Grist *et al.* (1961) reported "experimental evidence of such an occurrence" during studies with Cocksackie A7 virus on an adult pregnant merion. I suggest that the case of Baby C lends further support to this possibility.

Summary

Four cases of rubella in the newborn are reported. The differential diagnosis is briefly discussed.

Three of these cases are compared with similar reported cases of neonatal varicella. The fourth case occurred in a 12-day-old baby whose mother, having had rubella at an early age, was presumed, through known contact, to have had a subclinical attack prior to confinement. It is suggested that the baby was infected diaplacentally and was incubating the disease at birth. This case is compared with similar reported cases of prenatal infection by varicella, vaccinia, and variola.

It is suggested that the occurrence of such a case of prenatal incubation of rubella serves as a "missing link" between theory and evidence that previously suspected maternal subclinical rubella during the first trimester of pregnancy could be responsible for cases of subsequent rubella syndrome.

Theories on foetal viral immunity are briefly discussed.

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DOUBLE-BLIND TRIALS OF PROMAZINE IN LABOUR

BY

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A previous study (Matthews, 1961) of patients' responses in this obstetric unit included a questionnaire asking mothers to mention the most disturbing single symptom during labour. Pain accounted for 56% and fear or anxiety for 38%. Inquiry of the staff regarding the reason for administering drugs in labour showed that 49% were given for pain, 26% for fear, and 21% for restlessness or insomnia. This study therefore showed that there were three main groups of symptoms requiring relief in labour: (a) pain, (b) anxiety, and (c) restlessness and insomnia.

Unfortunately the same study made it clear that the drugs given for the relief of these symptoms were not always suitable, as the midwives were confused by the plethora of available agents. They were also governed by principles of treatment and timing of administration unrelated to the symptoms of the patient.

The first step in achieving rational treatment was to give drugs according to patients' requirements, and midwives were therefore asked to abide by the following three general principles: (1) concentrate on relief of symptoms in the first stage irrespective of degree of dilatation of the cervix or time since last drug administration; (2) record symptoms requiring relief and use appropriate agents; and (3) judge dosage according to severity of symptoms.

As a second step suitable drugs were chosen for the control of the major symptoms, enabling the attendant staff to become familiar with a few effective agents and to use them intelligently according to the symptomatic requirements of the patient.

The drugs needed to accomplish this aim in the first stage of labour were an analgesic for the pain group of symptoms, a tranquillizer for the fear group, and a hypnotic for the restlessness and insomnia group. Pethidine was chosen for the relief of pain and promethazine ("phenergan") for overcoming restlessness and insomnia.

After assessing a number of tranquillizers promazine hydrochloride ("sparine") emerged as the most satisfactory. As a result of these pilot trials it was decided to investigate the drug more thoroughly.

Toxicity Study

The first consideration of the drug given in labour must be its safety for both mother and child. Promazine has not been found to increase the length of labour when given intramuscularly or intravenously (Kuntze and Sison, 1957; Sprague, 1957; Pollock *et al.*, 1960). Transient slowing of contractions after intravenous administration with pethidine was noted by Bolton and Benson (1958) and by Pollock *et al.* (1960), but this was not shown by toco-

graphic studies of intravenous promazine alone (Caballero, 1958; MacVicar and Murray, 1960), and under some circumstances promazine appeared to shorten prolonged labour (Donald, 1959). The incidence of forceps delivery and post-partum haemorrhage was not increased. Evaluation of the effect of promazine on the foetus showed no evidence of foetal respiratory depression as assessed by Apgar ratings (Apgar *et al.*, 1958). The only deleterious effects of promazine were maternal tachycardia (Pollock *et al.*, 1960; Fitzpatrick *et al.*, 1960), occasional foetal tachycardia (MacVicar and Murray, 1960), and maternal hypotension (Sprague, 1957), but these appeared to be less frequent with intramuscular administration (Ponzi and Tiengo, 1958).

In order to confirm the apparent safety of intramuscular and oral promazine, a retrospective comparison was made between 500 consecutive cases admitted to the unit before promazine was used and a similar group of 500 mothers given promazine to allay fear and anxiety. In the first group, pethidine, chloral, dichloralphenazone, and methylpentynol were used, according to the individual preference of the attendant. In the second group, promazine was administered for fear and anxiety according to the patients' requirements, the usual dose being 50 to 100 mg. intramuscularly. The other drugs given were pethidine for pain and promethazine for insomnia.

After exclusion of patients not in labour, there were 495 patients in the promazine group and 498 controls. The groups were comparable with regard to age and parity, but

TABLE I.—Results of Retrospective Comparison
Delivery

Group	Total Patients	Surgical Induction	Epi-siotomy	Lacerations	Forceps	Caesarean Sections
Control	498	58	147	120	49	21
Promazine	495	41	155	113	42	23

Duration of Labour

Group	1st Stage (Hours)					2nd Stage (mins.)				3rd Stage (mins.)		
	<5	5–	10–	20–	40+	<15	15–	60–	120+	<15	15–	60+
Control	70	153	166	77	32	127	252	83	15	429	37	11
Promazine	60	150	171	85	29	102	261	87	22	433	33	6

Complications

Group	Maternal Tachycardia	Foetal Distress	Post-partum Blood Loss (oz.)			Manual Removal of Placenta	Vomiting	Intra-venous Fluids	Fresh Stillbirths
			<10	10–	20+				
Control	18	41	367	78	32	14	27	15	6
Promazine	32	42	368	78	26	10	5	3	5