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RUBELLA IN PREGNANCY AS AN AETIOLOGICAL FACTOR IN CONGENITAL MALFORMATION, STILLBIRTH, MISCARRIAGE AND ABORTION*

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PART I.

"This is the foul fiend Flibbertigibbet: he begins at curfew and walks till the first cock; he gives the web and pin, squints the eye and makes the harelip; mildews the white wheat and hurts the poor creature of earth."—*Shakespeare*

INTRODUCTION.

IN recent years there have been profound advances in our knowledge of antenatal paediatrics which, had he been alive to-day, would no doubt have afforded Ballantyne,[1] the pioneer in this field, considerable satisfaction and pleasure. Among these fundamental and fruitful observations one of the most important has been the discovery by Levine and his colleagues[2] of the relationship between the rhesus factor and haemolytic disease of the newborn, which has given a new significance to the influence of genetic factors on the developing embryo. In the past, little attention was paid to the part played in teratology by environmental factors, but here, too, outstanding progress has been made. Their role in the aetiology of congenital malformations has recently been ably reviewed by Warkany,[3] who divides them into nutritional, chemical, endocrine, actinic, mechanical and infectious types. It is impossible to single out all the investigators who have been responsible for this valuable work, but mention should be made of the demonstration by Hale, and by

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Warkany and his associates (for references see Warkany[3]) that specific types of congenital abnormality can be induced in animals by deprivation of their mothers during pregnancy of certain vitamins. Reference should be made, also, to the incrimination by Wolf[4] and his co-workers of the protozoon, Toxoplasma, as a cause of congenital defects.

The quotation with which it has seemed appropriate to head this essay is an example of the superstition which attributed congenital malformations to demoniacal agencies. One of the most subtle manifestations of "Flibbertigibbet" remained undetected until 1941. In the guise of rubella "Flibbertigibbet" stalked " . . . unseen by day as well as by night in the house, the school-room and crowded places . . . quite unsuspected and unfeared."[5] With malevolent cunning he made his main attack upon the embryo, realizing that months would elapse before the results of his perfidy were discovered and that it was unlikely that anyone would connect a trivial illness in the mother with severe congenital anomalies in the next generation. Emboldened, however, by the fact that his misdeeds had remained undetected for so long, he became over-confident and attacked an excessive number of susceptible, pregnant women in Australia during 1939 onwards. In consequence, in 1941 an unusual number of cases of congenital cataract were observed in Sydney, enabling Gregg,[6] with brilliant clinical acumen and epidemiological insight, to realize the significance of the phenomenon and to unmask the miscreant "Flibbertigibbet" in yet another of his manifold guises.

When a pregnant woman contracts an infectious disease, from the viewpoint of the embryo the author[7] envisages a number of possibilities:

(1) The embryo or foetus may be unaffected.

(2) As a result of the direct action of the noxa or the indirect effect of the associated pyrexia, the embryo or foetus may die, and an abortion, miscarriage or stillbirth may result according to the stage of gestation.

(3) Occurring early in pregnancy the infection may lead to congenital abnormalities, such as cardiac disease, as well as exerting a general deleterious effect on the embryo. The damaged embryo may then (*a*) be unable to survive to term and, as mentioned above, an abortion, miscarriage, or stillbirth will ensue; (*b*) live to term but be unable to survive the hazards of the birth process, so that it is stillborn; or (*c*) live to term and be born alive but congenitally defective.

On this basis the object of the present essay is to discuss the various effects of an attack of maternal rubella during gestation, the nature and frequency of the sequelae, their pathogenesis and the means of prevention.

Rubella and Congenital Malformations.

Australian Observations.

At the annual meeting of the Ophthalmological Society of Australia (British Medical Association) in 1941, N. McA. Gregg,[6] of Sydney, recorded a series of 78 cases of congenital cataract; in 44 of them a congenital lesion of the heart also was detected, in 10 the heart was apparently normal, and in the remainder the cardiac condition was not recorded. With the exception of 10 cases a history of maternal rubella was present, the infection occurring in 67 of the mothers during the first 3 months of pregnancy, and in one of them 3 months prior to conception.

Later, Gregg[8] described a further series of 7 cases and referred to 3 others; in 6 of the cases the mother had suffered from German measles during the first month of

pregnancy, in 3 during the second month, and in the remaining instance during the sixth month. The anomalies comprised cataract (8 cases), cardiac disease (7 cases), deaf-mutism (4 cases), dental defects (6 cases), mental deficiency (2 cases), and mongolism, buphthalmos and strabismus (each in 1 case).

With various colleagues the author[9, 10, 11, 12] carried out an extensive investigation in South Australia during the years 1942 to 1946 inclusive. The results have been published in a series of papers, in the last of which there is a summary of the researches as a whole. The total number of cases recorded was 120, in 101 of which there were congenital malformations. In 111 cases the maternal infection was diagnosed as rubella, in 1 as rubella and morbilli, in 2 as rubella and "soldier's" ("Woodside") throat, in 3 as rubella and mumps, in 1 as rubella and varicella, and in 2 as doubtful rubella. (In the 2 doubtful cases the diagnosis lay between rubella and morbilli). The following was the time of onset of the maternal infection in the cases followed by congenital abnormalities; first month of pregnancy, 19 cases; second month, 40 cases; third month, 21 cases; fourth month, 7 cases; fifth month, 4 cases; sixth month, 3 cases; seventh month, 2 cases; eighth month, 2 cases; ninth month, 1 case; month indeterminate, 2 cases. The various defects had the following frequencies; microcephaly, 62 cases; cardiac disease, 52 cases; deaf-mutism or deafness, 48 cases; cataract, 18 cases (12 bilateral, 6 unilateral); mental deficiency, 5 cases; strabismus and cryptorchidism, each in 4 cases; inguinal hernia, spina bifida occulta and high-arched palate, each in 3 cases; mongolism, speech defect, epilepsy, cleft palate (soft) and pyloric stenosis each in 2 cases; buphthalmos, hypospadias, hydrocele, bifid sternum, spastic diplegia, bilateral optic atrophy, lack of closure of the foetal fissure of the eye, naevus, Horner's syndrome, hemiparesis, umbilical hernia, obliteration of bile ducts, azygous lobe of lung, fusion of upper ends of radius and ulna and *talipes equinovarus* each in 1 case.

Evans[13, 14] examined 67 children of the series recorded by Swan and his associates; 30 suffered from congenital dental abnormalities, in 20 cases major in degree (caries was disregarded in this calculation). With 5 exceptions all the infants exhibited other congenital anomalies. For the most part the dental malformations were confined to children whose mothers had contracted rubella during the first 3 months of pregnancy. The main abnormalities included retardation of eruption of the deciduous teeth, dental caries and enamel hypoplasia. In addition there were 3 instances of congenital absence of isolated deciduous teeth and 4 of premature eruption of permanent teeth.

Of the 18 cases of deaf-mutism reported by Carruthers[15] in 2 the mother had suffered from German measles in the first month of gestation, in 10 in the second month, in 4 in the third month, in 1 in the fourth month and in 1 in the sixth month. Additional anomalies included obvious microcephaly in 3 instances, cardiac disease and strabismus each in 1 instance, and stunting of growth in 12 instances.

A Committee appointed by the Director-General of Public Health of New South Wales[16] investigated 136 cases of rubella in pregnancy in that State. In the 130 instances in which there were congenital defects, the maternal infection was contracted in 13 cases in the first month of pregnancy, in 50 in the second month, in 41 in the third month, and in 18 in the fourth month, while in 8 cases the time of onset was indeterminate. The malformations included 111 of deaf-mutism, 38 of cardiac

disease, 22 of cataract (15 bilateral, 7 unilateral) and 1 of bilateral buphthalmos.

In Queensland, Winterbotham[17] investigated 34 congenital deaf-mutes whose mothers had suffered from German measles in all instances at some stage during the first 4 months of gestation. In 11 of the children a cardiac lesion was also present. Winterbotham produced strongly suggestive evidence of a relationship between the occurrence of rubella in epidemic form and increases in the congenital cardiac mortality-rate and in the incidence of congenital deafness.

In 1947 Patrick[18] of the Queensland School Health Services, by means of a questionnaire, conducted a survey of 7,822 out of a total of 21,509 children born in that State during 1941. Altogether there were 262 cases in which the mothers were certain that they had contracted German measles during that particular pregnancy. It was possible to examine 129 of the children clinically; 51 of them were stated to have congenital defects. (There is a discrepancy, however, between Table I and Table II in Patrick's article. In the former there are only 50 instances of malformation). In addition, a further 36 mothers stated that their children suffered from congenital anomalies. The following was the incidence of abnormalities: deafness, 53 cases; high-frequency deafness, 3 cases; mental deficiency or retardation, 10 cases; mongolism, 2 cases; cardiac disease, 11 cases; ocular defects, nature not stated, 8 cases; astigmatism, 2 cases; myopia, 1 case; refractive error, nature not stated, 1 case; strabismus, 1 case; cataract (one, left-sided), 2 cases; cleft palate, 1 case; and malformed right ear lobe, 1 case. Of 50 of the cases with defects, in 4 the mother had contracted rubella in the first month of gestation, in 7 in the second month, in 18 in the third month, in 9 in the fourth month, in 2 in the fifth month, in 1 in the sixth month, in 3 in the seventh month, and in 1 in the eighth month, while in 5 instances the time of onset of the disease was indeterminate. In at least 2 of the uncertain cases, however, the maternal infection occurred in the early months. Among 36 further children with malformations, 29 mothers stated that they had suffered from German measles at some stage during the first 4 months of pregnancy, 3 were uncertain with regard to the actual time and the remainder stated that they had contracted the disease after the fourth month.

American Observations

In the literature of the United States of America the first observations to appear were those of Reese,[19] who described 3 cases. In each instance the mother had suffered from rubella during the first month of pregnancy. The defects comprised 3 cases of cataract (2 bilateral, 1 unilateral), 3 of cardiac disease, 1 of microcephaly, 1 of pyloric stenosis and 1 of umbilical hernia.

Rones[20] recorded 3 cases of German measles in gestation, the infection occurring in 1 instance in the first month, in 1 in the second month and in 1 in the third month. Two infants suffered from bilateral cataract. One had unilateral buphthalmos. One of the children with cataracts also had a cardiac defect.

Erickson[21] reported 11 cases, in 9 of which the mother had contracted rubella in the first month of pregnancy, in 1 in the second month and in 1 in the third month. All the babies born subsequently exhibited defects; there were 9 instances of cataract (7 bilateral, 2 unilateral), 1 of microphthalmia without other apparent ocular defect, 1 of unilateral corneal opacity, 9 of cardiac disease and 2 (1 possible, 1 certain) of mental retardation.

Greenthal[22] described 2 cases, the infec-

tion occurring in both instances in the second month of gestation. One of the infants born subsequently suffered from deafness, the other from unilateral cataract, mental retardation and a cardiac anomaly.

In the 1 instance recorded by Perera[23] the mother, who had suffered from German measles in the second month of pregnancy, later gave birth to a baby with unilateral cataract and cardiac disease.

The report of Adams[24] dealt with 2 cases, in one instance following rubella in the mother in the first month of gestation and in the other in the second month. Both infants exhibited cataract (1 bilateral, 1 unilateral) and cardiac disease; 1 also was mentally deficient and there was suggestive evidence of Madelung's deformity.

In the case described by Altmann and Dingmann[25] maternal German measles had occurred towards the end of the second month of pregnancy. The baby born subsequently had a unilateral cataract and was deaf.

In the 2 cases recorded by de Roetth and Greene[26] both mothers had contracted rubella in the second month of pregnancy, and both later gave birth to infants who suffered from bilateral cataract; in addition 1 was microcephalic and the other had a cardiac lesion.

Long and Danielson[27] studied 6 cases, in 4 of which maternal German measles had been diagnosed in the first month of gestation and in the remaining 2 instances in the second month. The following was the incidence of the anomalies: cataract, 6 cases (3 bilateral, 3 unilateral); cardiac disease, 6 cases; and bilateral cryptorchidism, *talipes valgus,* penile hypospadias, bilateral dacryostenosis, and strabismus, each in 1 case.

In the series of 5 cases investigated by Conte, McCammon and Christie,[28] 1 mother had suffered from rubella in the first month of pregnancy, 2 in the second month, 1 in the third month and 1 in the seventh month. The malformations in the babies born subsequently included 4 instances of bilateral cataract, 4 of cardiac disease, 1 of mongolism, 4 of cerebral aplasia and 2 of microcephaly.

Albaugh[29] described 7 cases, German measles occurring in the mother during gestation in 3 instances in the first month, in 2 in the second month, and in 2 in the third month. The congenital defects consisted of 6 cases of cataract (all bilateral) 6 of cardiac disease, 5 of microcephaly, 2 of umbilical hernia, 1 of pyloric stenosis and 1 of cryptorchidism.

With one exception (first month) all the mothers in the 5 examples recorded by Krause[30] had suffered from rubella during the second month of pregnancy. The congenital abnormalities comprised cataract in 5 cases (3 bilateral, 2 unilateral), cardiac disease in 3 cases, cerebral agenesis with mental retardation in 2 cases, mental retardation in 1, deaf-mutism in 1, spina bifida in 1, displacement of the fourth toes in 1 and dental aplasia in 1 case.

Only 2 of the mothers in the series of 12 cases reported by Fox and Bortin[31] gave birth to abnormal babies. In one instance the maternal infection with German measles had occurred in the first month of gestation and in the other in the second month. In both instances the infants were hydrocephalic; one was stillborn, the other was a "blue baby". In the latter the hydrocephalus receded spontaneously, and at the time of preparation of the report the infant was perfectly normal.

Aycock and Ingalls[32] studied 6 cases of congenital malformation following rubella in pregnancy, in one instance in the first month and in the remainder in the second month. The frequency of anomalies was as follows: cardiac disease, 3 cases; deafness, 2 cases; mental retardation, 2 cases; and cleft palate and cataract, each in 1 case.

In the 2 examples described by Guerry,[33] 1 mother had suffered from German measles in the second month of gestation, the other in the third month. One infant exhibited unilateral buphthalmos, the other bilateral buphthalmos together with bilateral cataract, cardiac disease and mental retardation.

Goar and Potts[34] recorded 6 cases. The time of contraction of rubella by the mothers during pregnancy was as follows: first month, 3 cases; second month, 2 cases; and third month, 1 case. All the infants born subsequently suffered from cataract (5 bilateral, 1 unilateral) and 5 of the 6 from cardiac disease. Other defects noted, each in one instance, were deafness and mental retardation.

Hopkins[35] investigated 11 cases of congenital deaf-mutism, following maternal German measles. The cases included one of twins. In 2 instances the infection had been diagnosed during the first month of gestation, in 2 during the second month, in 3 during the fourth month and in 2 during the sixth month. In the remaining cases the disease had occurred in one early in pregnancy and in the other in either the second or third month. Other defects encountered were cardiac disease in 4 instances, strabismus in 3 instances, mental retardation (certain in 2, probable in 1, and possible in 3 instances) and blindness, cataract and poor muscular co-ordination each in 1 instance.

Prendergast[36] made a survey in California by means of a questionnaire of the frequency of malformations among children whose mothers had had rubella during the first 3 months of pregnancy. Replies were received from 37 ophthalmologists, 24 paediatricians and 32 obstetricians. Undoubtedly, as Prendergast pointed out, there was some duplication of the data which are analyzed in the following table.

	Number of cases
A. *Ocular Defects*	
Cataract (reported by ophthalmologist)	40
Cataract (reported by paediatrician)	35
Cataract (reported by obstetrician)	5
Congenital glaucoma (reported by ophthalmologist)	2
Strabismus (reported by ophthalmologist)	1
Microphthalmos (reported by paediatrician)	4
Pigmented retina (reported by paediatrician)	2
Corneal opacity (reported by paediatrician)	1
B. *Cardiac Defects*	
Lesion (reported by paediatrician)	27
Lesion (reported by obstetrician)	5
C. *Miscellaneous Anomalies*	
Mental retardation (reported by paediatrician)	3
Mental retardation (reported by obstetrician)	1
Severe anaemia (reported by paediatrician)	1
Purpura (reported by paediatrician)	1
Microcephaly (reported by paediatrician)	1
Hypospadias (reported by paediatrician)	1
Cleft palate (reported by paediatrician)	1
Inguinal hernia (reported by paediatrician)	1

Dogramaci and Green[37] reported 5 cases of congenital heart disease following German measles in pregnancy. The infection had occurred in 2 cases in the first month and in the remainder in the third month. Additional abnormalities included 4 instances of cataract (3 bilateral, 1 unilateral), 1 of cleft palate and 1 of malformation of the right fourth rib.

Friedman and Cohen[38] described a case in which the mother developed an exanthem, which may have been rubella, in the second month of gestation. The infant born subsequently exhibited bilateral cataract, mental retardation and microcephaly. Autopsy revealed agenesis of the corpus callosum, the anterior commissure, the fornix and the upper motor neurones. In addition there was hydrocephalus, mild diffuse subcortical sclerosis, scarring of the kidneys with focal agenesis and mild scarring of the pancreas and thyroid.

Ingalls and Davies[39] noted a case of mongolism associated with maternal German measles in the second month of pregnancy.

Later, Ingalls[40] referred to another example of mongolism, communicated to him by Benda. In this case the mother had contracted rubella towards the end of the first month of gestation.

Ober, Horton and Feemster[41] reported 7 cases. In 2 instances the mother had suffered from German measles in the first month of pregnancy, in 2 in the second month, in 1 in the third month and in 1 in the sixth month. In the remaining case the time of onset of the infection was uncertain. The following was the incidence of defects: bilateral cataract, 3 cases; cardiac disease, 4 cases; and deafness, microcephaly and strabismus each in 1 case.

English Observations.

The first cases to be recorded in England were those by Simpson.[42] One mother had contracted rubella in the second month and the other in the third month of gestation. Both babies were born with congenital cataract and cardiac disease.

Martin[43, 44] drew attention to 36 cases of congenital deafness in which there was a history of maternal German measles at some stage during the first 4 months of pregnancy. Some of the children also had ocular and cardiac abnormalities.

A further case was studied by Hughes.[45] The mother, who had suffered from rubella during the second month of gestation, later gave birth to a baby who had unilateral cataract, deaf-mutism, cardiac disease, mental retardation and probable microcephaly.

Bower[46] reported 2 cases. In both instances the mothers had contracted German measles during the second month of pregnancy. Both infants exhibited deafness, cardiac disease and microcephaly. In addition in one instance there was bilateral cataract, and in the other the anterior fontanelle was exceptionally large at birth.

An anonymous medical practitioner[47] developed rubella during the third month of gestation. The infant born subsequently suffered from amyotonia, blue extremities and a bulging fontanelle. No visual, auditory or cardiac defect was detected. Death occurred at the age of 7 months from pneumococcal meningitis. The author refers to another case of congenital nerve deafness and "aphasia" in a child of 5 years, whose mother stated that she had had German measles at the seventh month of that particular pregnancy.

The only extensive and detailed investigation to be carried out so far in England is that by Clayton-Jones.[48] He collected 20 cases of deafness, of which 9 were also included in Martin's series.[43, 44] Rubella had occurred in the mother in 5 instances during the second month of gestation, in 2, in either the second or third month, in 4 in the third month, in 6 in either the third or fourth month and in 3 during the fourth month. Additional anomalies noted in the 9 children examined clinically were microcephaly in 6, jaw deformities in 2, strabismus in 1, and possible cardiac disease in 1.

Bell[49] observed 1 case in which the mother had suffered from German measles in the first month of pregnancy. The congenital abnormalities in the infant included bilateral cataract and deafness.

Pirrie[50] reported 1 case of congenital bilateral cataract, deafness and cardiac disease following the contraction of rubella by the mother in the first month of gestation.

L'Etang[51] referred to an example of congenital deaf-mutism in a male aged 65 years whose "mother always insisted it was due to the fact that during pregnancy she suffered from German measles."

Swiss Observations.

Franceschetti and Bourquin[52] studied 5 cases, of which in 2 the mothers had contracted rubella at the beginning of pregnancy, in 1 during the first month, in 1 during the second month, and in 1 during the third month. The defects comprised cataract in 4 instances (binocular in 3, monocular in 1), central "pseudo-retinitis pigmentosa" in 2, *talipes valgus* in 2, and cardiac disease, deafness, microcephaly and hypospadias each in 1.

Finnish Observations.

Zewi[53] described 2 cases. The mothers had suffered from German measles in the first and second months of gestation, respectively. One baby had bilateral cataract, the other bilateral buphthalmos; both had cardiac disease and mental retardation.

Swedish Observations.

Grönvall and Selander[54] investigated 7 cases of congenital malformation following maternal rubella in pregnancy. In 2 instances the diagnosis of the infection was almost, but not absolutely, certain. In 4 cases the mother had contracted the disease in the first month of gestation, in 1 in either the first or second month, in 1 in the second month and in 1 in the fifth month. The anomalies included cataract in 3 instances (1 bilateral, 1 right-sided, and 1 left-sided) accompanied in all by microphthalmos, pigmentary degeneration of the retina in 2, deafness in 4 (complete in 2, partial in 2), misshapen conchae in 1, cardiac disease in 4, mental retardation in 4 (1 slight), pigmented naevi (2 in the thoracic region) in 3, and dental defect in 1.

Norwegian Observations.

Hagelsteen[55] reported 2 cases; one mother had suffered from German measles in the first month and the other in the fourth month of pregnancy. In the former instance the infant born subsequently had a unilateral cataract and cardiac disease, in the latter the child had a deformed face, atresia of the auditory canal and an absent zygomatic arch.

Danish Observations.

Bardram and Braenstrup[56] recorded 8 cases, in 1 of which the baby was stillborn. In 4 rubella was contracted by the mother in the first month of gestation, in 3 in the second month and in 1 in the third month. The congenital defects included 7 cases (5 bilateral, 2 unilateral) of cataract, associated in 3 with microphthalmos, 1 case of bilateral buphthalmos, 3 of pigmentary degeneration of the retina, 1 of incomplete coloboma of the iris, 5 cases of cardiac disease, 1 case of a peculiarly long trunk, 1 of long fingers and toes and 1 of telangiectasis of the nose.

Review of the Investigations.

Nature of the Exanthematous Disease.

In his original paper Gregg[6] suggested that in some instances the exanthem might have been a toxic erythema associated with a severe upper respiratory tract infection of unusual character, then rife in military camps, and known as Ingleburn, Puckapunyal or Woodside throat, and which Gregg thought might be streptococcal in origin. Swan and his colleagues[9] could find no evidence in support of this view.

In Australia "... the 1940 'German measles' epidemic differed greatly from the ordinary virus infection bearing that name."[6] Often the illness was severe in character. In Sydney, for instance, the average stay in hospital of 4 days for patients suffering from rubella was doubled. "The swelling of the glands of the neck, the sore throat, the involvement of the wrist and ankle joints and the general constitutional disturbance were all very pronounced."[6]

Gregg's findings with regard to the

severity of the disease are borne out by the detailed analysis of the symptomatology undertaken by Swan and his associates.[9, 10, 11, 12] About half the mothers suffered from preliminary symptoms. Similar symptoms occurred concomitantly with the rash. They included general malaise, extreme tiredness, lassitude or sleepiness, pains in the limbs, back and neck, widespread aching, anorexia, nausea and vomiting, shivering, sneezing, pyrexia, sore throat and postauricular lymphadenitis.

The exanthem usually consisted of a fine, pin-point, slightly raised, non-irritating rash, pink in colour, which resembled heat-rash or prickly heat. There was evidence, however, in favour of Gregg's claim that the rash was occasionally pleomorphic. As a rule the exanthem began on the face, neck and chest and became general. For the most part it lasted from 3 to 4 days.

Postauricular or cervical lymphadenitis or both were present in 60 of the 118 cases and photophobia or soreness of the eyes in one-third of the cases. In approximately one-sixth of the mothers arthritis occurred.

In 68 of the 118 mothers the infection had been diagnosed as German measles by medical practitioners. A history of contact with relatives or friends who had been diagnosed as suffering from rubella by medical practitioners was elicited from about 20 more of the mothers, so that in approximately three-quarters of the cases of the series described by us[12] the diagnosis was supported medically. In the series of 136 cases reported by the New South Wales Committee[16] medical confirmation of the diagnosis was obtained in 38 cases. Confirmation was obtained also in 13 of the series of 20 cases investigated by Clayton-Jones.[48]

There is now general agreement that the exanthem was a manifestation of German measles as exemplified by Parsons[57] in his Blair-Bell Memorial Lecture. He says, "In my opinion, it should be accepted that the disease was rubella . . ."

There is evidence,[5, 10, 11, 19, 52] however, that the alteration in the character of the disease to a more severe type was not confined to Australia.

Nevertheless, the severity of the illness in the mother did not appear to be of any significance. Study of the available data failed to establish any relation between the degree of intensity of the maternal infection and the extent and severity of the congenital abnormalities.[10, 15, 16, 48]

Relation of the Time of Contraction of Rubella during Pregnancy and the Occurrence of Congenital Malformations.

In his original paper, Gregg[6] noted that in each instance the mother had suffered from the " . . . disease early in her pregnancy, most frequently in the first or second month." Swan and his collaborators[9] concluded that the "critical period" for the development of congenital defects was the first 3 months of gestation. Further work,[16, 58] however, extended the upper limit of the "critical period" to the end of the fourth month. In agreement with this view, a survey of cases of congenital abnormality following German measles[8, 12, 16, 18-35, 37-42, 45-56] shows that (Table I), of a total of 435 cases, in 389 the infection manifested itself at some stage during the first 4 months of pregnancy. Adding to these, 7 cases[12, 18, 35, 52] classified in Table I as "indeterminate," in which, though no precise information was available, the disease was known to have occurred within the same period of pregnancy, together with 67 cases reported by Gregg,[6] 29 further cases referred to by Patrick[18] and 27 recorded by Martin[44] (9 of her cases were discarded because they are included in Clayton-Jones's figures) out of a grand total of 558

TABLE I.

Relationship between the Time of Contraction of Rubella during Pregnancy and the Occurrence of Congenital Malformations in the Infants born subsequently.

Source	Month of pregnancy									Month indeterminate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
(8)	6	3	–	–	–	1	–	–	–	–	10
(12)	19	40	21	7	4	3	2	2	1	2	101
(16)	13	50	41	18	–	–	–	–	–	8	130
(18)	4	7	18	9	2	1	3	1	–	5	50
(19)	3	–	–	–	–	–	–	–	–	–	3
(20)	1	1	1	–	–	–	–	–	–	–	3
(21)	9	1	1	–	–	–	–	–	–	–	11
(22)	–	2	–	–	–	–	–	–	–	–	2
(23)	–	1	–	–	–	–	–	–	–	–	1
(24)	1	1	–	–	–	–	–	–	–	–	2
(25)	–	1	–	–	–	–	–	–	–	–	1
(26)	–	2	–	–	–	–	–	–	–	–	2
(27)	4	2	–	–	–	–	–	–	–	–	6
(28)	1	2	1	–	–	–	1	–	–	–	5
(29)	3	2	2	–	–	–	–	–	–	–	7
(30)	1	4	–	–	–	–	–	–	–	–	5
(31)	1	1	–	–	–	–	–	–	–	–	2
(32)	1	5	–	–	–	–	–	–	–	–	6
(33)	–	1	1	–	–	–	–	–	–	–	2
(34)	3	2	1	–	–	–	–	–	–	–	6
(35)	2	2	1	3	–	2	–	–	–	1	11
(37)	2	–	3	–	–	–	–	–	–	–	5
(38)	–	1	–	–	–	–	–	–	–	–	1
(39)	–	1	–	–	–	–	–	–	–	–	1
(40)	1	–	–	–	–	–	–	–	–	–	1
(41)	2	2	1	–	–	1	–	–	–	1	7
(42)	–	1	1	–	–	–	–	–	–	–	2
(45)	–	1	–	–	–	–	–	–	–	–	1
(46)	–	2	–	–	–	–	–	–	–	–	2
(47)	–	–	1	–	–	–	1	–	–	–	2
(48)	–	5	9	6	–	–	–	–	–	–	20
(49)	1	–	–	–	–	–	–	–	–	–	1
(50)	1	–	–	–	–	–	–	–	–	–	1
(51)	–	–	–	–	–	–	–	–	–	1	1
(52)	1	1	1	–	–	–	–	–	–	2	5
(53)	1	1	–	–	–	–	–	–	–	–	2
(54)	4	2	–	–	1	–	–	–	–	–	7
(55)	1	–	–	1	–	–	–	–	–	–	2
(56)	4	3	1	–	–	–	–	–	–	–	8
Total	90	150	105	44	7	8	7	3	1	20	435

cases with congenital malformations, in 519 the mother had contracted rubella in the first 4 months of pregnancy. This is equivalent to a percentage of 93.0 (approximately).

NATURE OF THE CONGENITAL DEFECTS.

Subsequent workers have fully confirmed Gregg's dictum[6] that many of the infants were " . . . of small size, ill-nourished and difficult to feed." Swan[58] noted that the average birth-weight of 45 infants with congenital anomalies was 5 pounds 11 ounces (2,580 g.), whereas in 16 normal babies (whose mothers had also suffered from rubella during gestation) it was 6 pounds 12¾ ounces (3,083 g.). Similarly in 18 babies with congenital malfor-

mations described by Carruthers[15] the average birth-weight was about 5 pounds 14 ounces (2,665 g.), in 34 recorded by Swan and Tostevin[11] it was 6 pounds $2\frac{1}{2}$ ounces (2,793 g.), in 130 reported by the New South Wales Committee[16] it was 5 pounds 15 ounces (2,693 g.), in 6 observed by Long and Danielson[27] it was about 5 pounds 7 ounces (2,466 g.), in 5 described by Conte and others[28] it was about 4 pounds 15 ounces (2,240 g.), and in 12 investigated by Clayton-Jones[48] it was 5 pounds $15\frac{3}{4}$ ounces (2,715 g.).

This retardation in physical development was maintained as the children grew older, many of them being stunted in stature. Often they were late in sitting up and in walking. (Illustrative cases appear in the paper by Swan and his colleagues.[12])

Eye defects. Up to the time of composition of this essay, 289 examples of cataract have been reported[6, 8-12, 16, 18-30, 32-38, 41, 42, 45, 46, 49, 50, 52-56]. The relation between the time of onset of rubella during gestation and the occurrence of congenital cataract, and of cataract accompanied by deaf-mutism in the infants born subsequently is shown in Tables II and III, respectively. It will be noted in Table II that cases of cataract are virtually limited to infants whose mothers had suffered from German measles in the first 3 months of pregnancy, and that the highest incidence of cases is in the first month. Cases of cataract occurring con-

TABLE II.

Relationship between Time of Onset of Rubella during Pregnancy and the Occurrence of Congenital Cataract in the Infants born subsequently.

Source	Month of pregnancy									Month indeterminate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
(8)	4	–	–	–	–	1	–	–	–	–	5
(12)	9	6	1	–	–	–	–	–	–	–	16
(16)*	4	8	2	–	–	–	–	–	–	–	14
(18)	–	–	–	–	–	–	–	1	–	1	2
(19)	3	–	–	–	–	–	–	–	–	–	3
(20)	1	1	–	–	–	–	–	–	–	–	2
(21)	8	1	–	–	–	–	–	–	–	–	9
(22)	–	1	–	–	–	–	–	–	–	–	1
(23)	–	1	–	–	–	–	–	–	–	–	1
(24)	1	1	–	–	–	–	–	–	–	–	2
(26)	–	2	–	–	–	–	–	–	–	–	2
(27)	4	2	–	–	–	–	–	–	–	–	6
(28)	1	2	–	–	–	–	1	–	–	–	4
(29)	3	2	1	–	–	–	–	–	–	–	6
(30)	–	4	–	–	–	–	–	–	–	–	4
(33)	–	1	–	–	–	–	–	–	–	–	1
(34)	2	2	1	–	–	–	–	–	–	–	5
(37)	1	–	3	–	–	–	–	–	–	–	4
(38)	–	1	–	–	–	–	–	–	–	–	1
(41)	2	1	–	–	–	–	–	–	–	–	3
(42)	–	1	1	–	–	–	–	–	–	–	2
(52)	1	–	1	–	–	–	–	–	–	2	4
(53)	1	–	–	–	–	–	–	–	–	–	1
(54)	2	–	–	–	–	–	–	–	–	–	2
(55)	1	–	–	–	–	–	–	–	–	–	1
(56)	4	2	1	–	–	–	–	–	–	–	7
Total	52	39	11	–	–	1	1	1	–	3	108

*One of these cases may be a case of buphthalmos.

TABLE III.
Relationship between Time of Onset of Rubella during Pregnancy and the Occurrence of Congenital Cataract concomitantly with Deaf-mutism in the Infants born subsequently.

Source	Month of pregnancy									Month indeterminate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
(8)	1	2	–	–	–	–	–	–	–	–	3
(12)	1	1	–	–	–	–	–	–	–	–	2
(16)*	6	3	–	–	–	–	–	–	–	–	9
(25)	–	1	–	–	–	–	–	–	–	–	1
(30)	1	–	–	–	–	–	–	–	–	–	1
(32)	–	1	–	–	–	–	–	–	–	–	1
(34)	1	–	–	–	–	–	–	–	–	–	1
(35)	–	1	–	–	–	–	–	–	–	–	1
(45)	–	1	–	–	–	–	–	–	–	–	1
(46)	–	1	–	–	–	–	–	–	–	–	1
(49)	1	–	–	–	–	–	–	–	–	–	1
(50)	1	–	–	–	–	–	–	–	–	–	1
(54)	1	–	–	–	–	–	–	–	–	–	1
Total	13	11	–	–	–	–	–	–	–	–	24

* One of these cases may be a case of buphthalmos

comitantly with deaf-mutism were confined to the first 2 months of gestation (Table III). Of the 204 cases of cataract, in 150 the defect was binocular and in 54 monocular. Of 35 unilateral cases, in 21 the cataract was left-sided and in 14 it was right-sided (*see* Table IV).

A photograph of a child showing the typical clinical appearance of the cataract is shown on page 46 of Warkany's article.[3]

The admirable description of the cataract which Gregg[6] gave in his first paper, and which has remained unsurpassed, has gained wide acceptance. He characterized the condition as being "subtotal". There were two main types, which Gregg[6] occasionally observed in one and the same patient. "In one, a dense, white, often pearly, central opacity was surrounded by a zone of less dense opacity of smoky appearance and finally by a narrow peripheral ring of clear cortex through which a red reflex was obtainable. In the other, the contrast between the central and intermediate zones was less pronounced so that the cataract was uniform throughout."[59] The graphic account of the lesion given by Barham Black (*see* Swan and his associates[9]) is also worth quoting. He observed that "the opacity . . . had the appearance of a flattened dense white disc in which six radiating lines were visible. These lines were presumed to be the two lens Y's superimposed, giving an appearance like a minute white starfish. If good mydriasis was obtained, a clear zone was visible peripheral to the opacity. The whole lens was very small . . ." A somewhat similar appearance was noted by Gregg[8] in his second series of cases. He stated that the cataract resembled "a three-bladed aeroplane propeller". As observed originally by Gregg,[6, 8] and later by Rones[20] and Adams,[24] progressive increase in the size of the cataracts sometimes took place.

Ocular defects occurring in association with cataract. Microphthalmos was a frequent concomitant;[6, 8-12, 16, 19, 21, 26, 27, 29; 30, 33, 34, 52-54, 56] Gregg noted it in approximately two-thirds of his monocular cases. Swan and his associates[9] compared the volumes of the two eyes obtained at post-mortem on a child with a unilateral defect.

The affected globe was only three-quarters the size of the other.

A number of investigators stressed the shallowness of the anterior chamber.[6, 8, 9, 19, 26, 29, 33] In the single instance reported by Perera[23] the anterior chambers were normal in depth.

The reaction of the pupil to light was variable. Some authors[6, 19, 26, 27, 30, 33] found that it was poor or sluggish. (In Guerry's case,[33] however, glaucoma was also present). Other workers[27, 29, 34] obtained a brisk reaction.

Atrophy of the iris was occasionally ob-

TABLE IV.
Analysis of Localization of Cases of Cataract and of the Incidence of Associated Microphthalmos.

	Cataract						
		Unilateral			Whether unilateral or bilateral not stated		
Source	Bilateral	Right-sided	Left-sided	Not stated		Total number	Associated microphthalmos
(6)	62	–	–	16	–	78*	In 10 out of 16 unilateral cases
(8)	5	2	1	–	–	8	6
(12)	12	2	4	–	–	18	6
(16)	15	–	5	2	–	22	5
(18)	–	–	1	–	1	2	–
(19)	2	1	–	–	–	3	3
(20)	2	–	–	–	–	2	–
(21)	7	–	2	–	–	9	2
(22)	–	1	–	–	–	1	–
(23)	–	1	–	–	–	1	–
(24)	1	–	1	–	–	2	–
(25)	–	1	–	–	–	1	–
(26)	2	–	–	–	–	2	1
(27)	3	2	1	–	–	6	6
(28)	4	–	–	–	–	4	–
(29)	6	–	–	–	–	6	3
(30)	3	–	2	–	–	5	1
(32)	–	–	–	–	1	1	–
(33)	1	–	–	–	–	1	1
(34)	5	–	1	–	–	6	6
(35)	–	–	–	–	1	1	–
(36)	–	–	–	–	80	80	–
(37)	3	–	1	–	–	4	–
(38)	1	–	–	–	1	1	–
(41)	3	–	–	–	–	3	–
(42)	–	–	–	–	2	2	–
(45)	–	–	1	–	–	1	–
(46)	1	–	–	–	–	1	–
(49)	1	–	–	–	–	1	–
(50)	1	–	–	–	–	1	–
(52)	3	1	–	–	–	4	1
(53)	1	–	–	–	–	1	1
(54)	1	1	1	–	–	3	3
(55)	–	–	–	1	–	1	–
(56)	5	2	–	–	–	7	3
Total	150	14	21	19	85	289	58

* In 10 of these cases there was no definite history of rubella in pregnancy and in one the maternal infection occurred 3 months before conception.

served.[6, 8, 16, 30] On the other hand, Reese[19] considered that the irides in his cases were normal.

Sometimes difficulty in obtaining mydriasis was experienced.[6, 8, 9, 11, 53] Occasionally, but not always,[27, 34] good results followed the use of homatropine or paredrine hydrobromide. Albaugh[29] employed 2 per cent neosynephrin with satisfactory results.

Bardram and Braenstrup[56] noted 1 case of incomplete coloboma of the iris.

Gregg[6] has described 3 cases, and Krause[30] 1, in which corneal opacities were present, although ocular tension was normal. After some days or weeks the corneae cleared to reveal the typical cataracts. In Guerry's patient,[33] however, there was concomitant glaucoma.

In 2 cases[6, 30] subluxation of the cataractous lenses was evident.

Nystagmus of an ocular type and indicative of lack of development of fixation was absent at birth, but appeared if there was delay in treatment or lack of response to it.[6, 8-10, 16, 19, 27-29, 33, 34, 45, 46]

Strabismus was occasionally encountered.[9, 16, 27, 29, 33-35, 46]

In a few cases[8, 16] optic atrophy was present.

Swan[58] described a $2\frac{1}{2}$-month-old foetus in which there was lack of closure of the choroidal or foetal fissure.

Nasolacrimal stenosis was sometimes noted.[6, 16, 27]

In one instance[16] pigmentary changes of the fundus oculi were detected.

Krause[30] recorded anterior uveitis in 2 cases.

Ocular lesions in the absence of cataract. Probably the most important of these was buphthalmos. Cases were observed by Swan and his co-workers,[9] Gregg,[8] the New South Wales Committee,[16] Rones,[20] Guerry,[33] Prendergast,[36] Zewi,[53] and Bardram and Braenstrup.[56]

Pigmentary changes of the fundus oculi of a distinctive type have been described by many investigators.[6, 9, 16, 25, 27, 36, 52, 56; 63] Franceschetti and Bourquin[52] referred to the condition as central "pseudoretinitis pigmentosa."

Strabismus sometimes occurred.[8, 11, 12, 15, 18, 29, 35, 36, 41, 48]

In a few instances microphthalmos was present[8, 16, 21, 36] accompanied in one case by corneal opacity.[21]

Three authors[16, 18, 46] mention refractive errors.

In one instance nasolacrimal stenosis was observed.[10]

Other defects which manifested themselves rarely were nystagmus,[8] corneal opacity,[27, 30, 36] amaurosis,[35] amblyopia,[11, 8] atrophy of the iris,[8] optic atrophy,[8, 12, 27, 56] doubtful coloboma,[6] and vitreous opacities[27]

Pathology of the ocular lesions. I was able to give the first description of the pathological changes.[60] I found that the cataracts consisted of a central "nuclear" portion which was amorphous and stained poorly and which had apparently undergone necrosis *en masse,* and a cortical zone, most evident in the equatorial region, composed of degenerate cells which were attempting to form new lens fibres.

Terry[61] examined the eyes of a baby suffering from bilateral cataract following rubella in the mother during the third month of pregnancy. The most interesting change in the lens was the fact that the foetal nucleus almost touched the anterior pole " . . . indicating that the lens fibres in some manner were prevented from growing forward and inserting themselves in front of the nucleus." Other changes included small retinal ganglion cells, poor development of the rods and cones, a poorly formed meshwork in the filtration angle, failure of atrophy to occur in the iris in

order to produce crypts, and lack of development of the ciliary body.

Swan[58] studied the eyes of a 2½-month-old foetus (pregnancy had been terminated because the mother had suffered from rubella late in the second month). The left eye was normal, but the right, which was smaller in size, showed considerable disorganization of structure. The lens stained poorly, and was cataractous and distorted. The hyaloid vessels were reduced in number and the foetal fissure, which was closed in the left eye, was still open.

The pathological examination performed by Cordes and Barber[62] was limited to a single eye obtained as the result of a therapeutic abortion of a 7- or 8-week-old embryo following the occurrence of maternal German measles in the sixth week of gestation. While the lens was retarded in its development and differentiation, the posterior segment of the globe seemed normal. At the anterior pole of the lens the cells of the subcapsular epithelium were distorted and disorientated. Although the primary fibres had elongated they failed completely to fill the cavity of the lens vesicle. The fibres were swollen and stained palely; at their anterior ends vacuoles were evident. These authors suggested that the cataract was due to the toxic agent, transported by means of the amniotic fluid, acting directly on the lens. They pointed out that after the 3-months stage this structure becomes protected by the development of the lids and of Descemet's and Bowman's membranes. This hypothesis affords a reasonable explanation of the virtual confinement of rubella cataract to cases in which the infection manifested itself in the first 3 months of pregnancy. On the other hand, the occurrence of cardiac disease, deaf-mutism, and microcephaly would seem to indicate that there is a widespread attack on the embryo by the noxa via the blood-stream.

In the case of bilateral cataract described by Friedman and Cohen,[38] in which maternal rubella was doubtful, lesions in the lenses were largely confined to the central two-thirds of the posterior subcapsular region, the changes including wrinkling of the capsule, the presence of minute vacuoles and irregular clefts and swelling of the lens fibres sometimes associated with metamorphosis into Morgagnian bodies. In addition some subcapsular vacuolation was evident in the equatorial region. The nucleus of each lens was unaffected.

Bardram and Braenstrup[56] recorded the ocular changes in a stillborn infant who exhibited bilateral cataract as the result of rubella during the second month of pregnancy. Histologically the cornea, anterior chamber, iris and ciliary body were normal. The lens capsule was folded irregularly, and beneath it, both anteriorly and posteriorly, an eosinophilic liquid cleft was visible. In the cortex posteriorly there was complete destruction of lens fibres with formation of Morgagnian globules; anteriorly the changes were less pronounced. The central portion of the lens was sclerosed and stained intensely, so that the cataract was hypermature in type.

Treatment of the ocular lesions. With regard to cataract in most instances discission was performed and the resultant aphakia corrected by spectacles. For the most part repeated needling was necessary because of the slowness of absorption of the cataract. Only occasionally was it rapid. Goar and Potts[34] advocated the through-and-through discission of Ziegler. On account of the toughness of the lens capsule, and of the frequency with which discission eventually leads to retinal detachment, de Roetth and Greene[26] performed lens extraction with satisfactory results. Similar results were obtained by Albaugh[29] from employment of the Robbin's suction method.

In a case of buphthalmos, Swan and his collaborators[9] noted considerable improvement after trephining. In this regard Gregg[8] and Zewi,[53] were less fortunate. Because of posterior synechiae and friability of the iris, Guerry[33] was unsuccessful in performing an iris-inclusion operation. He substituted a modified Lagrange operation with good results. In the second eye, however, a similar manoeuvre led to little corneal clearing.

In a single case of amblyopia associated with concomitant strabismus, there was no improvement in visual acuity from occlusion.[11] On the other hand, Gregg[8] noted good results from atropinization.

Deaf-mutism. This abnormality was first recorded by Swan and others[9] and discovered independently by Gregg and by Tostevin within 6 months of each other (*see* Swan and Tostevin[11]).

Up to the present time 327 cases have been reported.[8, 12, 15-18, 22, 25, 30, 32, 34, 35, 41, 44-52, 54] (In the present calculations the 18 cases of Carruthers[15] have not been counted on the grounds that they also appear in the figures of the New South Wales Committee.[16] There is probably some overlapping in the examples reported by Winterbotham[17] and by Patrick.[18]) In addition Patrick has observed 3 cases of high-frequency deafness. The relation between the time of onset of rubella during gestation and the occurrence of congenital deaf-mutism, and of deaf-mutism accompanied by cataract, in the infants born subsequently is shown in Tables V and III, respectively. It will be observed (Table V) that the cases are virtually confined to infants whose mothers had suffered from the infection during the first 4 months of pregnancy, and that the highest incidence of cases is in the second and third months.

The incidence of deaf-mutism is probably greater than would appear from the published cases because many instances of congenital defect following maternal rubella were recorded before this abnormality would be readily detectable. In this regard Swan and others[12] on a follow-up examination of their earlier series of cases[9, 10] detected 4 additional cases of deaf-mutism.

The character of the deaf-mutism is

TABLE V.

Relationship between Time of Onset of Rubella, during Pregnancy and the Occurrence of Congenital Deaf-mutism in the Infants born subsequently.

Source	Month of Pregnancy									Month indeterminate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
(8)	–	1	–	–	–	–	–	–	–	–	1
(12)	4	25	13	3	–	–	–	–	–	1	46
(16)	2	38	37	17	–	–	–	–	–	8	102
(18)	2	7	16	6	1	–	2	–	–	3	37
(22)	–	1	–	–	–	–	–	–	–	–	1
(32)	–	1	–	–	–	–	–	–	–	–	1
(35)	2	1	1	3	–	2	–	–	–	1	10
(41)	–	–	1	–	–	–	–	–	–	–	1
(46)	–	1	–	–	–	–	–	–	–	–	1
(47)	–	–	–	–	–	–	1	–	–	–	1
(48)	–	5	9	6	–	–	–	–	–	–	20
(51)	–	–	–	–	–	–	–	–	–	1	1
(52)	–	1	–	–	–	–	–	–	–	–	1
(54)	1	2	–	–	–	–	–	–	–	–	3
Total	11	83	77	35	1	2	3	–	–	14	226

analyzed in the papers of Swan and his associates,[9-12] Carruthers,[15] the New South Wales Committee,[16] Patrick,[18] Hopkins[35] and Clayton-Jones.[48] Deafness was of the inner ear type. In general, it was not absolute and the children were able to hear loud, sharp noises, such as hand-clapping, the dropping of a tray, the banging of a door and a dog barking. High-pitched sounds, such as train whistles and the screaming of other children were also appreciated. Other noises to which the children responded were the ringing of a telephone, the wireless, motor-car horns and aeroplane engines. Few patients could hear the spoken voice. Many of the children vocalized but speech, when it existed, was usually monosyllabic. Occasionally, however, the children were able to say a few words.

Swan and his associates[9-12] gained the impression that high tones were better appreciated than low tones, but the audiograms of Clayton-Jones's series[48] failed to confirm this view, as the loss of hearing was as a rule fairly uniform throughout the frequency range.

On examination the external canal and ear drums were normal.[9-12, 16]

Grades of deafness. Swan and Tostevin[11] found that their 25 patients fell into 3 main groups. Three children were stone-deaf, 19 suffered from the characteristic type of deafness described above, and 3 were partially deaf and had speech defects which suggested that "islands" of deafness were present. Of 11 children reported by Hopkins[35] 6 were profoundly deaf and 5 were partially deaf. In 3 cases one ear was more affected than the other. In Clayton-Jones's series,[48] 3 cases were classified as severe, 3 as moderate and 1 as slight. Patrick[18] adopted the classification published in the "Report of the Committee of Inquiry into Problems Relating to Children with Defective Hearing."[64] It is as follows:

> Grade I. Children with defective hearing who can, nevertheless, without special arrangements of any kind, obtain proper benefit from the education provided in an ordinary school, elementary, secondary, or technical.
>
> Grade II. Children whose hearing is defective to such a degree that they require for their education special arrangements or facilities, but not the educational methods used for deaf children without naturally acquired speech or language. These facilities range from a favourable position in the ordinary school classroom to attendance at a special class or school.
>
> Grade IIA. Those children within Grade II who can make satisfactory progress in ordinary classes in ordinary schools provided they are given some help, whether by way of favourable position in class, by individual hearing aids, or by tuition in lip-reading.
>
> Grade IIB. Those children within Grade II who, even with the help of favourable position in class, individual hearing aids or tuition in lip-reading, fail to make satisfactory progress in ordinary classes in ordinary schools.
>
> Grade III. Children whose hearing is so defective and whose speech and language are so little developed that they require education by methods used for deaf children without naturally acquired speech or language. This grade includes the totally deaf.

Of 34 cases Patrick found that 27 belonged to Grade III, 2 to Grade IIB, 1 to Grade IIA, and 4 to Grade I.

Classification of deafness. Carruthers[15] "... considered that the cases belonged to Scheib's type of sacculo-cochlear degeneration which comprises 70 per cent of cases of congenital deaf-mutism. In this type the saccule and cochlea, especially the organ of Corti, show evidence of maldevelopment, while the vestibule and semicircular canals are more or less normal. Hearing is extremely poor, but usually

deafness is incomplete and the vestibular apparatus reacts to stimulation. In conformity with Carruthers' view is the fact that in the deaf-mutism resulting from maternal rubella the loss of hearing is only partial. Furthermore, in the 9 cases submitted by Carruthers to caloric stimulation, the vestibular apparatus gave an active though slightly reduced response. Likewise in Altmann and Dingmann's case the vestibular function was normal." (Swan[59])

Speech defect. Swan and his colleagues [11, 12] described 2 cases of speech defect which they attributed to the presence of small "islands" of deafness.

Pathology. Carruthers[15] examined the aural structures of an infant who died at the age of 6½ months. The mother had contracted rubella during the first month of pregnancy. The baby suffered from bilateral cataract and heart disease and was thought to be deaf. The general configuration of the middle ear, auditory ossicles and inner ear appeared to be normal, and the 8th nerve and spiral ganglion were well formed. The significant pathological feature was the complete absence of any differentiation of the primitive cells to form the organ of Corti. There was also lack of differentiation of the receptor end-organ known as the crista. As in the remainder of his cases labyrinthine function was normal, Carruthers attributed the defect in this particular case to the early stage of pregnancy at which the embryo was attacked.

Treatment. The treatment of the condition has comprised speech therapy together with the employment of hearing aids. In Australia, where a large number of cases exist, in almost every State special schools have been opened.

Cardiac malformations. So far 274 examples of congenital cardiac disease have been reported.[6, 8, 9-12, 16-24, 26-30, 32-37, 41, 42, 45, 46, 48, 50, 52-56] The relation between the time of onset of rubella during gestation and the occurrence of congenital heart disease in the infants born subsequently is shown in Table VI. The cases are virtually confined to the first 4 months of pregnancy with the highest incidence in the first and second months.

In Gregg's first paper,[6] Harper classified the cardiac defects as belonging to the acyanotic or potentially cyanotic groups. Her findings have been largely confirmed by subsequent investigators, although in recent years a few examples of the cyanotic type have been described.[29, 34, 37]

Gregg[8] and Swan[58] noted simultaneously that the anomaly was present more often in association with cataract than with deaf-mutism. Goode (*see* Swan and others[9]) observed that heart disease could appear as the sole abnormality.

When bruits were present, in the majority of instances they were harsh and rough in character and systolic in time. Occasionally, systolic-diastolic murmurs were met with; some of them were of the "machinery" type. For the most part the bruits were situated basally, and were maximal in the pulmonary area. Sometimes the murmurs were audible all over the precordium; in a few cases they were apical. In some instances a thrill was present. Now and then there was clinical evidence of cardiac enlargement. Often, but not always, there was confirmatory X-ray evidence of heart disease. On the other hand, occasional cases were encountered in which, although the clinical findings were negative, a cardiac lesion was detected on radiological or postmortem examination.[9, 11, 16]

The common defects were patent ductus arteriosus [6, 8, 9, 11, 16, 19, 23, 27, 37, 52, 55] and patent interventricular septum,[6, 9, 19, 22, 24, 27, 34, 35, 37, 45] but one case of Fallot's tetralogy[37] and a possible example of a bicuspid aortic valve with regurgitation[35] were also noted.

TABLE VI.

Relationship between Time of Onset of Rubella during Pregnancy and the Occurrence of Congenital Cardiac Defects in the Infants born subsequently.

Source	Month of Pregnancy									Month indeterminate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
(8)	5	2	–	–	–	–	–	–	–	–	7
(12)	10	18	14	4	2	–	2	1	–	1	52
(16)	11	16	8	3	–	–	–	–	–	–	38
(18)	1	1	2	3	–	–	–	–	–	2	9
(19)	3	–	–	–	–	–	–	–	–	–	3
(20)	1	–	–	–	–	–	–	–	–	–	1
(21)	7	1	1	–	–	–	–	–	–	–	9
(22)	–	1	–	–	–	–	–	–	–	–	1
(23)	–	1	–	–	–	–	–	–	–	–	1
(24)	1	1	–	–	–	–	–	–	–	–	2
(26)	–	1	–	–	–	–	–	–	–	–	1
(27)	5	1	–	–	–	–	–	–	–	–	6
(28)	1	2	1	–	–	–	–	–	–	–	4
(29)	3	1	2	–	–	–	–	–	–	–	6
(30)	–	3	–	–	–	–	–	–	–	–	3
(32)	1	2	–	–	–	–	–	–	–	–	3
(33)	–	1	–	–	–	–	–	–	–	–	1
(34)	3	1	1	–	–	–	–	–	–	–	5
(35)	1	2	–	–	–	–	–	–	–	1	4
(37)	2	–	3	–	–	–	–	–	–	–	5
(41)	1	2	–	–	–	–	–	–	–	1	4
(42)	–	1	1	–	–	–	–	–	–	–	2
(45)	–	1	–	–	–	–	–	–	–	–	1
(46)	–	2	–	–	–	–	–	–	–	–	2
(48)	–	–	1	–	–	–	–	–	–	–	1
(50)	1	–	–	–	–	–	–	–	–	–	1
(52)	1	–	–	–	–	–	–	–	–	–	1
(53)	1	1	–	–	–	–	–	–	–	–	2
(54)	3	1	–	–	–	–	–	–	–	–	4
(55)	1	–	–	–	–	–	–	–	–	–	1
(56)	3	1	1	–	–	–	–	–	–	–	5
Total	66	64	35	10	2	–	2	1	–	5	185

Pathology. Gregg[6] referred briefly to the autopsy findings in 3 subjects; in all the ductus arteriosus was widely patent and in one, additional lesions in the form of patency of the interventricular septum and of the foramen ovale were present.

In the 3 postmortem examinations described by Swan[60] in each instance the ductus arteriosus was widely patent and there was a variable degree of patency of the foramen ovale. In one case a defect of the interventricular septum was also observed. Microscopically, the well-defined elastic lamina and intimal mounds normally present in the ductus arteriosus were non-existent and signs of obliterative endarteritis were absent. At the margins of the septal defect there was occasional replacement of muscle fibres by connective tissue.

Treatment. In 2 cases[12, 16] the ductus arteriosus was successfully ligated, with subsequent considerable clinical improvement in the children. In the example reported by Dogramaci and Green,[37] although the ductus arteriosus was divided, the operation was complicated by the presence of a patent interventricular sep-

tum. An operation was performed by Dr. Blalock on the patient with Fallot's tetralogy.[37]

Microcephaly. The occurrence of this abnormality in association with maternal German measles was first noted by Swan.[59]

Swan and others[9-12] detected it in 62 out of 101 cases, the New South Wales Committee[16] in 44 out of 52 cases and Clayton-Jones[48] in 6 out of 9 cases. Albaugh[29] reported 5 examples and Conte and his associates[28] and Bower[46] each 2. A number of single instances have been described.[19, 26, 36, 38, 41, 45, 52] Excluding Carruther's cases on the grounds that they are included in the figures of the New South Wales Committee, a total of 128 cases has been recorded.

Mental deficiency or retardation. (Included under this heading are cases diagnosed as "cerebral aplasia" and "cerebral agenesis.")

In a personal communication to Swan and his collaborators,[9] Gregg stated that he considered all his patients were mentally retarded, but later he revised his opinion.

A total of 52 cases has been recorded, including 2 by Gregg,[8] 5 by Swan and his associates,[9-12] 3 by the New South Wales Committee,[16] 10 by Patrick,[18] 2 by Erickson,[21] 1 by Greenthal,[22] 1 by Adams,[24] 4 by Conte and others,[28] 3 by Krause,[30] 2 by Aycock and Ingalls,[32] 1 by Guerry,[33] 6 by Hopkins,[35] 4 by Prendergast,[36] 1 by Friedman and Cohen,[38] 1 by Hughes,[45] 2 by Zewi[53] and 4 by Grönvall and Selander.[54]

Mongolism. In all, 8 examples have been reported. Gregg[8] observed 1 case, Swan and his colleagues,[11, 12] 2, Patrick[18] 2, Conte and others[28] 1, Ingalls and Davies[39] 1, and Ingalls[40] 1.

Miscellaneous Abnormalities.

Skeletal system. The following defects were observed: large size of the anterior fontanelle of the skull, 5 cases;[6, 9, 24 46, 60] deformed face 1,[55] malformed ear lobe 1,[18] malformed conchae 1,[54] atresia of the auditory canal 1,[55] widely curved maxillary arch with gross narrowing of the mandibular arch 2,[48] absence of zygomatic arch 1,[55] high arched palate 4,[12, 38] a peculiarly long trunk 1,[56] spina bifida occulta 3,[11, 12] Spina bifida 1,[30] bifid sternum 1,[12] malformation of a rib 2,[11, 37] fusion of upper ends of radius and ulna 1,[2] Madelung's deformity 1,[24] arachnodactyly 2,[6, 56] dislocation of hip joint 1,[16] talipes valgus 3[27, 52] talipes equinovarus 2,[9, 16] talipes varus 1,[6] and displacement of fourth toes 1.[30]

Muscular system. The anomalies comprised amyotonia, 1 case;[47] poor muscular tone 2,[48] and poor muscular co-ordination 1.[35].

Nervous system. The defects included agenesis of the corpus callosum, 1 case,[38] hydrocephalus 2,[31] epilepsy 2,[12] spastic diplegia 1,[11] hemiparesis 1,[12] and Horner's Syndrome 1.[12]

Genito-urinary tract. The abnormalities consisted of cryptorchidism, in 6 cases,[12, 27, 29] hydrocele in 1,[12] bilobed kidney in 1,[6] bicornuate uterus in 1,[6] and hypospadias in 4.[9, 27, 36, 52]

In 3 postmortem examinations Swan[60] observed slight glomerular sclerosis. Later[58] he noted similar lesions in the kidneys of a baby whose mother had had a normal pregnancy, so that their precise significance in relation to rubella must await the examination of further material. Baar[65] states that: "endothelial proliferation and hyalinization in arterioles and glomeruli . . . proliferation in the parietal layer of Bowman's capsule and fusion with the tuft are frequently found in kidneys of newborn infants ('congenital glomerulosclerosis')."

Hernia. There were 4 cases each of inguinal hernia,[11, 12, 36] and of umbilical hernia.[12, 19, 29]

Respiratory system. The anomalies were limited to 1 case of azygous lobe of a lung.[12]

Digestive system. The malformations comprised 4 cases of pyloric stenosis,[11, 19, 29] and 1 of obliteration of the bile ducts.[10]

Palate. In 2 instances there was a cleft of the soft palate,[11, 12] and in 5 there was a complete cleft.[6, 18, 32, 36, 37]

Skin. In 5 cases a naevus was evident.[11, 54, 56] Dermatitis was noted "in a few cases."[6]

Blood diseases. These included 4 cases of anaemia,[21, 28, 36] and 1 of purpura.[36]

Dental defects. As mentioned earlier these defects were first described by Evans.[13, 14] This author's findings with regard to retardation of eruption of the deciduous teeth have been generally accepted.[8, 16, 18, 48] On the other hand, while in a few instances Evans[14] noted premature eruption of the permanent teeth, Haenke (*see* Patrick[18]) stated that the eruption of the 6-year molars was delayed. Clayton-Jones[48] considered that the eruption of the second dentition was normal.

Evans[13, 14] found a high incidence of dental caries in his patients and the New South Wales Committee[16] concluded that in their series it might be slightly above the normal average. On the other hand, neither Haenke nor Clayton-Jones[48] found any abnormal tendency to caries.

Dental hypoplasia, which was of frequent occurrence in Evans's cases, was also detected in greater incidence than normal by the New South Wales Committee[16] and by Haenke.

Krause[30] noted in 1 case that there was dental aplasia, and Grönvall and Selander[54] in 1 case that there was a dental defect.

Abnormalities of the dental arches, sometimes associated with crowning of the lower teeth and with high arched palate were mentioned by Evans,[13, 14] the New South Wales Committee[16] and Clayton-Jones.[48]

Congenital Deformities Following an Attack of Rubella Before Conception.

In his first paper Gregg[6] mentioned that in 1 of his cases of congenital cataract the onset of German measles in the mother was said to have occurred 3 months before conception. Subsequently Gregg[8] reported a further case in which a woman contracted rubella approximately 16 days before conception and gave birth to an infant who was a deaf-mute. Swan and his colleagues described a doubtful positive example[10] and later[11] 2 negative ones, in which the onset of the infection had occurred about 3 months, about 13 days, and about 6 days, respectively, before conception. Hall[66] recorded a case of congenital, bilateral cataract, cardiac disease and deaf-mutism subsequent to a "sharp attack" of German measles in the mother 6 weeks before the child was conceived. Sweet, in a personal communication to Wesselhoeft[5] refers to a woman who contracted rubella 10 days before conception. The infant born as a result of this pregnancy had bilateral hydrocephalus and cataract, patent ductus arteriosus and lived only 3 months.

Congenital Malformations Similar to those Described in Association with Rubella, in the Apparent Absence of Infection in Pregnancy.

A number of investigators have reported congenital abnormalities apparently identical with those occurring subsequent to maternal German measles, in which the mother denied infection during gestation. Gregg[6] described 10 cases, Swan and others[9] 3 cases (in only 1 was the resemblance pronounced), the New South Wales Committee[16] 9 cases, Carruthers[15] 5 cases, Goar and Potts[34] 1 case and Hopkins[35] 6 cases.

Abortions, Miscarriages and Stillbirths Following Maternal Rubella in Gestation.

Until recently attention was focused exclusively on the most striking result of an attack of German measles on the developing embryo, that is, on the congenital anomalies, and the possibility that the infection might also be a cause of intra-uterine death remained in the background. Gibson[67] referred to stillbirths in association with maternal rubella but gave no details, and The New South Wales Committee[16] suggested that in addition to congenital malformation some miscarriages and stillbirths might have occurred as a result of the maternal infection in that State.

Within the last 2 years a number of reports have accumulated which indicate that the suggestions of the Australian authors[16, 67] are not unfounded.

The relation between the time of onset of rubella during gestation and the occurrence of intra-uterine deaths (abortions, miscarriages and stillbirths) is shown in Table VII. Although no definite conclusions can be drawn from such a small series of cases, the figures suggest that as with congenital malformations the "critical period" is the first 4 months of pregnancy.

Four instances of abortion have been recorded. In the one described by Aycock and Ingalls[32] infection with rubella in the first month of gestation was followed by immediate death of the embryo and its extrusion during the sixth week. In Ober, Horton and Feemster's[41] case the infection occurred in the third month of pregnancy

Table VII.

Relationship between Time of Onset of Rubella during Pregnancy and the Occurrence of Intra-uterine Deaths (Abortions, Miscarriages and Stillbirths).

Source	Month of Pregnancy									Month indeterminate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
Abortions											
(32)	1	–	–	–	–	–	–	–	–	–	1
(41)	–	–	1	–	–	–	–	–	–	–	1
(54)	1	–	1	–	–	–	–	–	–	–	2
Total	2	–	2	–	–	–	–	–	–	–	4
Miscarriages											
(5)	–	1	2	–	–	–	–	–	–	–	3
(32)	–	1	–	1	–	–	–	–	–	–	2
(41)	2	–	1	1	–	–	–	–	–	–	4
Total	2	2	3	2	–	–	–	–	–	–	9
Stillbirths											
(7)	1	4	4	2	2	1	–	–	–	2	16
(31)	1	–	–	–	–	–	–	–	–	–	1
(32)	–	–	–	–	–	–	–	–	–	1	1
(34)	1	–	–	–	–	–	–	–	–	–	1
(41)	–	2	–	–	–	–	1	1	–	–	4
(54)	–	–	–	1	–	–	–	–	–	–	1
(56)	–	1	–	–	–	–	–	–	–	–	1
Total	3	7	4	3	2	1	1	1	–	3	25
Grand total											
Total	7	9	9	5	2	1	1	1	–	3	38

and in Grönvall and Selander's[54] 2 cases in the first and third months, respectively.

Up to the present time a total of 9 miscarriages has been reported, including 3 by Wesselhoeft,[5] 2 by Aycock and Ingalls[32] and 4 by Ober, Horton and Feemster.[41] In 2 instances the mother had suffered from German measles in the first month of pregnancy, in 2 in the second month, in 3 in the third month and in 2 in the fourth month.

In all, 25 stillbirths have been described; they comprise 1 by Fox and Bortin,[81] 1 by Aycock and Ingalls,[32] 1 by Goar and Potts,[34] 4 by Ober, Horton and Feemster,[41] 1 by Grönvall and Selander,[54] 16 by Swan,[7] and 1 by Bardram and Braenstrup.[56] (The baby examined by Fox and Bortin was hydrocephalic and the one studied by Bardram and Braenstrup had bilateral cataract. The infant investigated by Goar and Potts was a twin; its fellow, born alive, suffered from bilateral cataract and cardiac disease.) The time of onset of the maternal infection during gestation was as follows: first month 3 cases, second month 7, third month 4, fourth month 3, fifth month 2, sixth month 1, seventh month 1, eighth month 1, and month indeterminate 3.

Absence of Congenital Defects Following Rubella in Pregnancy.

Swan and others[12] have recorded 17 cases, the New South Wales Committee,[16] 6, Patrick[18] 79, Conte, McCammon and Christie[28] 1, Fox and Bortin[31] 10, Aycock and Ingalls[32] 3, Ober, Horton and Feemster[41] 38, Bell[49] 1, Grönvall and Selander[54] 24, and Councilman[68] 1.

Analysis of the 180 cases showed that the duration of pregnancy at the time of the infection was as follows: first month 11 cases, second month 26, third month 31, fourth month 23, fifth month 28, sixth month 20, seventh month 16, eighth month 7, ninth month 8, month indeterminate 10 (*see* Table VIII).

In addition Prendergast[36] reported 4 cases, all of which occurred in the first trimester of pregnancy.

TABLE VIII.

Relationship between Time of Onset of Rubella during Pregnancy and the absence of Congenital Defects in the Infants born subsequently.

Source	Month of Pregnancy									Month indeterminate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
(12)	1	2	2	1	3	3	3	1	1	–	17
(16)	1	–	1	1	2	–	1	–	–	–	6
(18)	6	10	14	9	11	10	4	5	1	9	79
(28)	–	–	–	–	–	–	–	–	1	–	1
(31)	–	4	3	1	–	–	1	–	1	–	10*
(32)	–	1	–	1	–	–	–	–	1	–	3
(41)	1	4	6	4	9	5	6	–	2	1	38
(49)	–	–	1	–	–	–	–	–	–	–	1
(54)	2	5	4	6	3	2	1	–	1	–	24
(68)	–	–	–	–	–	–	–	1	–	–	1
Total	11	26	31	23	28	20	16	7	8	10	180

* Includes one case of twins.

RUBELLA IN PREGNANCY AS AN AETIOLOGICAL FACTOR IN CONGENITAL MALFORMATION, STILLBIRTH, MISCARRIAGE AND ABORTION

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PART II

PATHOGENESIS

Gregg[6] suggested that the mechanism of production of the congenital abnormalities was a toxic or infective process leading to a partial arrest of development.

The fundamental principle in the pathogenesis, however, was first recognized by Swan and his colleagues.[9] They cited evidence to show that in both birds and mammals embryonic cells are much more susceptible than are adult tissues to virus and other infections, and concluded: " . . . Is it not logical to assume . . . that the human embryo possesses the same susceptibility to infectious agents as avian and other mamalian embryos, and that the aetiological factor of German measles, after penetrating the chorionic barrier, is capable of producing severe lesions in the embryo, while the same infection in the adult tissues of the mother leads only to a minor illness?"

The virtual confinement of congenital malformations to infants whose mothers had contracted rubella during the first trimester of pregnancy, led Swan and his associates[9] to conclude that it was only during this period that the embryonic cells manifested a heightened susceptibility. Alternatively, they surmised that with the formation of the placenta at the end of the third month of gestation, the barriers between mother and embryo might become less penetrable by the virus. Of the two alternatives, they favoured the first.

At autopsy on 3 babies dying from congenital anomalies subsequent to maternal rubella, in addition to other defects Swan[60] found cardiac disease. He quoted Bedford and Brown[69] to the effect that the critical period for the development of congenital cardiac defects " is from the fifth to the eighth week of intra-uterine life, during which the septa are forming, the bulbus cordis is undergoing involution, and torsion of the great vessels is taking place." Swan continued, " it is of interest to note that in the present cases this was the precise period during which the mothers suffered from rubella, and that one infant (Case I) exhibited an inter-ventricular septal defect."

Hurst[70] suggested that it would be possible to correlate the congenital heart and lenticular lesions if it were assumed that the virus acted primarily on vascular tissue and that the cataract was secondary to involvement of the hyaloid vessels.

On the basis of the results of experimental embryology, Mann[71] stated that, " . . . in man the most important determining factor for the effect of a maternally transmitted disease is the time of its action,

only those cells which are in active division at the time being affected. Fully formed organs and quiescent primordia alike tend to escape. The more fully differentiated the foetus, the more the disease will resemble the same disease in the adult and vice versa."

Using the data compiled by Swan and his co-workers,[9] Mann found that there was a definite parallelism between the time of onset of the maternal infection and the known times of active proliferation of the lenticular, cochlear and cardiac primordia.

Attempts to Correlate the Data on Rubella and Congenital Malformations with Stockard's Conclusions

This aspect of the pathogenesis has been elaborated by Swan and Tostevin,[11] who endeavoured to ascertain how far the data on rubella could be correlated with the conclusions arrived at by Stockard[72] as a result of his experiments with the common minnow, *Fundulus heteroclitus*. Stockard's first conclusion was summarized by Swan and Tostevin[11] as follows: "The type of abnormality is determined by the particular developmental "moment" at which the noxa acts. At different periods in the development of the ovum, certain primordia are undergoing rapid proliferation, and may be thought of as developing at a rate entirely in excess of the general developmental rate of the embryo. At such periods these primordia are peculiarly susceptible to unfavourable influences, while only slight or no ill effects may be suffered by the embryo as a whole."

Swan and Tostevin pointed out that earlier, with various colleagues,[9, 10] they had found that the average duration of pregnancy at the time of contraction of rubella in 11 mothers whose children were deaf-mutes was 2.3 months, whereas in 15 mothers whose babies had cataract it was 1.4 months, and had therefore argued that the type of congenital defect was to some extent dependent on the time of onset of the maternal infection. Furthermore, they described a case in which the development of rubella in the seventh or eighth week of gestation was followed by lack of closure of the foetal (choroidal) fissure. As this fissure normally closes during the seventh week, in this instance, too, the anomaly and the time of attack by the virus were complementary. Swan and Tostevin referred to the criticism by Carruthers[15] that while the stage of onset of the maternal infection was of significance in determining the nature of the developmental anomalies, the taking of an average was misleading. Deaf-mutism, for example, might result from the contraction of rubella in several of the earlier months of gestation. Swan and Tostevin[11] drew the obvious conclusion that in human beings the anlagen of the various organs have relatively long "critical moments." In general, they believed that for the optic primordium it was the first 3 months of pregnancy and for the cochlear anlage it was the second, third and fourth months. [As far as the cochlear primordium is concerned, later statistics (see Tables III and V) indicate that it also susceptible to the virus during the first month.] They also suggested that averages such as they had drawn might indicate the period of greatest susceptibility of a particular primordium to the virus. The authors[11] drew attention to several discrepancies; for instance, the primordia of the lenses, having reached the same stage of growth, might reasonably be expected to be equally susceptible or immune to the virus, and yet monocular cases of cataract occurred. Similarly, in a case of lack of closure of the foetal fissure of the eye, the condition was unilateral. Finally, in referring to another point in Stockard's first conclusion, namely, that while at the

"critical moments" certain anlagen are particularly sensitive, only slight or no ill-effects are experienced by the embryo in general, Swan and Tostevin[11] pointed out that one of the components of the post-rubella syndrome is stunting of growth, indicating that although the main attack of the virus is borne by the specialized cells of certain primordia there is a general but slighter involvement of the less specialized cells of the skeletal tissues.

The second conclusion of Stockard was summarized as follows: "The earlier the arrest the more numerous will be the types of defect found, and the later the arrest the more limited the variety of deformities, since there are fewer organs to be affected during their rapidly proliferating primary stages."

Swan and Tostevin regarded their own evidence as equivocal, pointing out that: ". . . whether the mother contracted the disease in the first month or second month of pregnancy seemed to be of little significance in determining the number of congenital defects in the children born subsequently."

They drew attention, however, to the investigations of the New South Wales Committee[16] who found that when the anomalies, eye disease, deaf-mutism and cardiac disease were present concomitantly, in all instances the maternal infection had occurred within the first 2 months of gestation and in 6 of the 8 mothers during the first month. Conversely, Swan and Tostevin considered it worthy of note that both the New South Wales Committee and themselves had observed cases in which single congenital defects had resulted from the contraction of German measles in the first month of pregnancy. In support of Stockard's second conclusion, Swan and Tostevin cited the following statement of Carruthers:[15] "I am inclined to think that the importance of the stage of pregnancy at which infection occurs is that, if it is in the first six weeks, foetal damage will be widespread and may include the eyes, both divisions of the ears, the heart and perhaps many other parts. After the sixth week the eyes may escape, the heart may be spared and the semi-circular canals may become normally developed; but the cochlea is still likely to be damaged, and growth may be retarded. After the third month damage to the foetus is rare."

Nevertheless, they concluded that some modification of Carruthers' dictum was necessary, because their own statistics and those of the New South Wales Committee[16] showed that deaf-mutism subsequent to the contraction of rubella in the first month of gestation was relatively infrequent [this has not been entirely borne out by later statistics (see Tables III and V)] and that congenital abnormalities were a relatively common sequel to maternal German measles in the fourth month.

Swan and Tostevin summarized Stockard's third conclusion as follows: "If development is arrested or retarded at a stage when no unusually rapid changes are taking place, a comparatively quiescent moment during which all parts are developing, but during which no particular or important part is proliferating at an excessively high rate, the embryo may escape injury."

They believed that this conclusion provided a logical explanation of the failure of congenital malformations to develop when the mothers contracted rubella after the fourth month of pregnancy. Although conceding that if such "moments of indifference", as Stockard called them, manifested themselves early in gestation, they would serve to account for the instances in which the occurrence of German measles in the initial stages did not lead to congenital defects, Swan and Tostevin believed that in such cases it was equally possible that

the virus failed to penetrate the barriers between the mother and the embryo and, therefore, had no chance to attack the latter.

Stockard's fourth conclusion was summarized by Swan and Tostevin as follows: "The same abnormality may be induced in embryos by a great number of different noxae."

They drew attention to Ida Mann's statement that " . . . it may well be found that a variety of other causes operating during the first six weeks (of pregnancy) may produce congenital cataract and heart disease. If this result is found to be absolutely specific for rubella it will be surprising from an embryologist's point of view."

Their own researches, carried out with various colleagues, on congenital anomalies in association with maternal morbilli, mumps, varicella, herpes zoster, and scarlet fever during gestation had produced equivocal results, and the question whether infectious diseases other than German measles were responsible for the development of congenital defects remained an open one. They agreed, however, " with Ida Mann that an important factor in determining such a relationship may prove to be the penetrability or otherwise of the barrier between mother and embryo."

In summing up, Swan and Tostevin emphasized that although there was considerable parallelism between the results of experimental teratology and the data on post-rubella anomalies, the analogy should not be drawn too far. It was important to realize that investigators such as Stockard were concerned with inanimate noxae, whereas they were " . . . dealing with a living virus, able both to proliferate and to attack living cells." They considered that this fact might be of considerable significance in the explanation of such divergences as might later become apparent.

Swan and Tostevin pointed out that not only were the anomalies the result of arrested development as Stockard had maintained but that contrary to his conception there was some pathological evidence in support of Mall's view that the arrests were accompanied by actual destruction of tissue.

Elective Affinity of the Virus of Rubella for Tissues Derived from one or other of the Three Primary Germ Layers.

Swan and his co-workers[12] explored the possibility that the virus might have an elective affinity for tissues taking origin from certain of the three primary germ layers. From a survey of the available evidence they found that the brunt of the pathological process was borne by ectodermal and mesodermal derivatives and that there was little involvement of entodermal ones. The ectodermal structures affected included the lens and cochlea, the retina, iris and optic nerve, the central nervous system (mental retardation and epilepsy), the skin (dermatitis) and the distal urethra (penile hypospadias). Lesions of mesodermal structures comprised cardiac defects, microcephaly, generalized stunting of the skeleton, high-arched palate, large size of the anterior fontanelle, spina bifida occulta, bifid sternum, fusion of the upper ends of the radius and ulna, and talipes equinovarus. The investigators concluded that there was no significant difference in the susceptibility to the rubella virus of primordia taking origin from ectoderm or mesoderm, rather it appeared to be dependent on the degree of specialization of the cells.

The Role of the Adrenals in the Production of Congenital Malformations Subsequent to Maternal Rubella.

Brown[73] claimed that the primary attack of the virus of rubella was on the embryonic adrenal cortex, and that the various

components of the post-rubella syndrome, for example deaf-mutism, cardiac disease and microcephaly, were secondary to adrenal cortical insufficiency. He admitted, however, that the lenticular, corneal, and vitreous opacities were probably the result of the direct action of the virus on these tissues or on their respective primordia.

This hypothesis will not withstand critical examination,[74] for the gland develops relatively late. While the anlage of the cortex is present during the second month of intra-uterine life of the embryo, no trace of the medulla is detectable until the end of the sixth week. Moreover, no secretion of adrenalin is possible until the termination of the organogenetic period at the end of the third month, and no lipoid or chromaffin reaction can be obtained before the sixth month. On this basis, "it seems very unlikely . . . that the regulation of organogenesis (which is disturbed by rubella) is related to any endocrine activity comparable to that of post-natal life. The genes, the organisers, and the growth gradients themselves are mapping out the endocrine organs during the first three months, and the problem is one of experimental embryology, not adult pathology. If hypoplastic adrenals are found in post-rubella infants (and in Swan's cases they were not) are they not likely to be an additional manifestation of the suppressive action of the virus on rapidly differentiating structures rather than the primary lesion?"[74]

Congenital Deformities Following an Attack of Rubella Before Conception.

At the present time the pathogenesis is obscure. Swan and his co-workers[10] postulated that subsequent to the original infection it would be possible for the virus to remain latent in the maternal tissues, and that with the advent of the embryo the virus would be reactivated on coming into contact with the rapidly dividing and more susceptible embryonic cells. From then on the pathogenesis would be similar to that obtaining in cases in which the infection was contracted during gestation. In support of their hypothesis they cited evidence to show that various viruses have the power of persistence for relatively long periods of time in the tissues of the original host. That such a power of persistence may be exhibited also by rubella virus is suggested by the occurrence of relapse in this disease. The nature of these relapses has been discussed by Wesselhoeft.[5]

Congenital Malformations Similar to Those Described in Association with Rubella in the Apparent Absence of Infection in Pregnancy.

To account for such anomalies it has been suggested that they are the result of sub-clinical attacks of German measles.[10, 15, 16, 32, 34]

Abortions, Miscarriages and Stillbirths Following Maternal Rubella in Gestation.

Swan[7] envisaged two main mechanisms: (1) the immediate death of the embryo or foetus, as a result of the direct action of the virus or the indirect effect of the concomitant pyrexia, with its subsequent extrusion and (2) the production of congenital abnormalities of such character as to interfere with the viability of the embryo so that either it died before the completion of the term of intra-uterine existence or was . . . "unable to survive the hazards of the birth process." Depending on the time of death of the foetus (using the term in the broad sense) an abortion, miscarriage or stillbirth would result.

Absence of Congenital Defects Following Rubella in Pregnancy.

An obvious explanation is that some of the cases may be the result of wrong diagnosis. The differential diagnosis has been discussed by Swan and his associates[9] and by Wesselhoeft.[5] It is evident that diagnosis may sometimes prove difficult. In this regard Wesselhoeft makes the following statement: "From my hospital experience I am aware of so many cases erroneously diagnosed as rubella that I cannot be too sure of the accuracy of the State reports on this disease."

In cases in which the diagnosis of rubella appeared beyond dispute, it has been suggested that either the virus failed to penetrate the barriers between the mother and foetus or that it attacked the latter at a period designated by Stockard as "a moment of indifference."[11]

Prevention.

Unfortunately, the obvious method of avoidance of exposure to infection is subject to a number of difficulties. In the first place, as in morbilli, the period of infectivity precedes the exanthem, so that even the prompt isolation of the patient at its first appearance fails to prevent the transmission of the disease to others.[5] Secondly, many mothers do not know of the dangers of rubella in pregnancy, and even if they did, they may be quite unaware that they are pregnant, and unwittingly may run the risk of infection during the most vulnerable stage of gestation.

Erickson[21] and Aycock and Ingalls[32] maintained that females should not be allowed to pass through childhood without having had German measles, and advocated deliberate exposure to infection at an opportune time. Greenthal[22] believed that the risk of a severe attack or even of complications such as encephalitis was justified. But unless such exposure were carried out with strict precautions with regard to isolation, it would entail the risk of infection of the mothers of the children, a proportion of whom would be pregnant.

The use of convalescent serum both as a prophylactic and a curative measure was first suggested by Swan and his collaborators.[9] With regard to the former procedure, Barenberg and others[75] have presented presumptive evidence of its efficacy, but as far as the latter is concerned, it seems unlikely that once the virus has gained access to the embryo, that convalescent serum, even in repeated doses, would have any effect.

The prophylactic administration of immune gamma globulin was originally recommended by Strong.[76] Aycock and Ingalls[32] have pointed out, however, that available clinical experience has not established its efficacy. There have been a number of instances of apparent failure of this substance to prevent the disease. These authors cited 3 instances in which rubella developed about a fortnight after the injection of gamma globulin.

The isolation of the virus with the object of preparing a protective vaccine was first suggested by Swan and his associates.[9] As Wesselhoeft,[5] however, points out: "Until a vaccine of modified rubella virus that will not give rise to a communicable form of the disease and yet will afford a permanent immunity has been perfected, the complicated problem of protecting pregnant mothers from contracting rubella will remain."

Termination of Pregnancy.

The controversial question whether or not women who contract rubella in the early months of gestation should be submitted to therapeutic abortion was first raised by Swan and his colleagues.[9] They claimed that the only reasons which would

justify the induction of labour were the preservation of either the life of the mother or the life of the child, and that therefore, as far as German measles was concerned, there were no legal grounds for such an act. They also feared that if the law were amended to allow for such a contingency, abuses might creep in.

The matter has been debated since then on religious, legal and social grounds; [5, 11, 18, 19, 21, 22, 32, 34, 45, 77] clearly it is fraught with difficulties. From these view-points the following statement of Aycock and Ingalls[32] is apposite: "Such a far-reaching question can be approached with wisdom only when there are adequate statistical studies to establish the specific risks of infection at all stages of pregnancy. Knowledge from such studies would have to be interpreted not only in terms of actual risk of congenital anomalies but as well in terms of the 'health of the mother' in continuing a pregnancy with such a known risk and finally in terms of an informed public opinion."

The crux of the matter is the frequency with which congenital abnormalities will occur subsequent to an attack of rubella in the various stages of gestation. In 1943 Swan and his associates[9] concluded that "... on the available evidence, when a woman contracts rubella within the first two months of pregnancy, it would appear that the chances of her giving birth to a congenitally defective child are in the region of 100 per cent, and if she contracts rubella in the third month they are about 50 per cent. ... There is still slight likelihood that the child will be congenitally defective if rubella is contracted after the third month of pregnancy."

Unfortunately the data gathered by Swan and his co-workers are subject to the criticism that because German measles is not notifiable in South Australia, they were forced to rely upon the cases being reported to them. Under the aegis of the British Medical Association, all the medical practitioners in the State were circularized and there was an enthusiastic response which enabled the investigators to collect both positive cases, viz. those in which there were congenital malformations, and negative ones, viz. those in which the child born subsequently was normal. Nevertheless, as they[78] themselves admitted, there was no doubt a tendency for the more spectacular positive cases to be reported to the neglect of the negative ones.

In an attempt to obtain more precise statistics Fox and Bortin[31] surveyed 22,226 cases of rubella notified in the city of Milwaukee during the years 1942 to 1944 inclusive. Of 152 married women, 11 were pregnant when they suffered from the disease. Only 2 of the women gave birth to infants with a congenital abnormality, which in each instance took the form of hydrocephalus. The mothers had contracted German measles in the first and second months of gestation respectively. Of the mothers who bore normal children (in one instance, twins), 3 had had rubella in the second month, 3 in the third month, 1 in the fourth month, 1 in the seventh month and 1 in the ninth month.

Adopting the method of Fox and Bortin, Aycock and Ingalls[32] found among 1,300 cases of rubella reported to the Boards of Health of two Massachusetts communities, 4 cases in which the disease occurred during pregnancy. In 2 instances the infection was contracted in the second month (1 infant suffered from mental retardation), in 1 in the fourth month and in 1 in the ninth month. With the one exception, the children were normal. By working back from known cases of congenital abnormality the authors detected 5 cases of rubella in pregnancy which had occurred during the same epidemic. In 1 case the infection had manifested itself in the first

month of gestation and in 4 in the second month. Only one of the 5 cases had been reported to the Board of Health. In addition they discovered 2 cases of spontaneous abortion subsequent to maternal German measles; in neither instance had the infection been notified. It is evident, therefore, that even studies based on cases reported to departments of health have their limitations because of the inefficiency of notification of an apparently innocuous disease like rubella.

A similar survey carried out by Ober and his collaborators[41]* resulted in the collection of 54 cases of rubella in pregnancy. They found that of 5 women who had contracted the infection during the first month of gestation, 2 aborted, 2 had infants with congenital anomalies and 1 had a normal infant, so that 80 per cent of the offspring were either lost or defective. As a result of the disease in the second month, 2 babies were stillborn, 2 had congenital defects and 4 were normal; thus 50 per cent were either lost or defective. In the third month there were 2 abortions and 1 congenital malformation together with 6 normal infants so that one third of the offspring were lost or defective. In the fourth month there were 1 abortion, 1 infant with a doubtful congenital abnormality and 3 normal infants, thus the incidence of offspring lost or defective was 40 per cent. In the later months of gestation there were 1 minor defect (sixth month), and 2 stillbirths (1, seventh month; 1, eighth month). Finally there was one case of congenital anomaly in which the month of pregnancy at which German measles occurred was uncertain. Altogether in the 54 cases, there were 37 normal infants, 8 infants with congenital defects (1, perhaps 2, cases doubtful) and 9 cases in which pregnancy ended in abortion, miscarriage or stillbirth. In addition Ober and his associates sent questionnaires to physicians in Massachusetts, which led to the collection of a further 8 cases. In all instances the infection had occurred in the first trimester of gestation. Five of the babies born subsequently suffered from congenital malformations, 2 babies were normal and there was 1 abortion. Finally the authors combined the 54 cases of their series with the 11 cases reported by Fox and Bortin and the 4 cases recorded by Aycock and Ingalls, all of which were collected under similar conditions. The proportion of offspring lost or defective was as follows: first trimester, 50 per cent; second trimester and third trimester each about 14 per cent.

[Incidentally, Ober and his colleagues were unable to account for the small number of cases reported in the later months of gestation. In this connexion, Clayton-Jones[79] states that " . . . the most likely explanation seems to be that women do not go out and about much late in pregnancy, and so escape contact infection."]

In an attempt " . . . to assess accurately the risk that a mother suffering from rubella during pregnancy will produce a child with an abnormality" Patrick[18] conducted a survey by means of a questionnaire of 6 year-old children who had commenced school in Queensland in 1947. Of 129 cases in which the children were examined clinically, the following was the time of onset of the maternal infection (the number of cases in which the infection was followed by congenital abnormalities is shown in parentheses): first month of pregnancy, 10(4); second month, 17(7); third month, 32(18); fourth month, 18(9); fifth month, 13(2); sixth month, 11(1); seventh month, (7(3); eighth month, 6(1); ninth month, 1(0); month indeterminate, 14(5). From his figures it would appear that the risk of a mother giving birth to a

* Some of the cases classified by these authors as abortions are actually miscarriages.

TABLE IX.

Analysis of Incidence of Congenitally Defective Infants, Intra-uterine Deaths and Normal Infants and their Percentage Frequency following Maternal Rubella in the Various Months of pregnancy.

Result of infection in pregnancy	Month of pregnancy									Month indeter-minate	Total
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th		
Congenitally defective infants	89* (83.2%)	149* (81.0%)	105 (72.4%)	44 (61.1%)	7 (18.9%)	8 (27.6%)	7 (29.2%)	3 (27.3%)	1 (11.1%)	20 (60.6%)	433 (66.5%)
Intra-uterine deaths	7 (6.5%)	9 (4.9%)	9 (6.2%)	5 (7.0%)	2 (5.4%)	1 (3.4%)	1 (4.2%)	1 (9.1%)	0 (0%)	3 (9.1%)	38 (5.8%)
Normal infants	11 (10.3%)	26 (14.1%)	31 (21.4%)	23 (31.9%)	28 (75.7%)	20 (69.0%)	16 (66.6%)	7 (63.6%)	8 (88.9%)	10 (30.3%)	180 (27.7%)
Total	107	184	145	72	37	29	24	11	9	33	651

* One case is omitted so that it will not be included both under "Congenitally Defective Infants" and "Intra-uterine Deaths."

congenitally defective infant following the contraction of rubella in the first trimester of gestation are about 49.2 and in the first four months are 49.4 per cent. Patrick's evidence, however, is open to a number of serious objections. As the author, himself, points out, not only had 7 years elapsed between the contraction of the infection and the time when the questionnaire was answered, but in most instances the disease was apparently self-diagnosed. Furthermore the direct question whether or not the mother suffered from German measles in pregnancy was asked. Finally the investigation takes no account of infants with congenital defects of sufficient gravity to lead either to death or to preclude attendance even at the special schools included in Patrick's survey. In this connexion it may be mentioned that death occurred early in postnatal life in more than 15 out of Gregg's first series of 78 cases[80] and in 9 out of 101 congenitally defective babies recorded by Swan and his associates.[12]

A survey of the available evidence (embodied in Tables I, VII and VIII, and combined in Table IX) shows that the risk of a mother giving birth to a child with congenital anomalies following the contraction of rubella in the first 4 months of pregnancy ranges from 83.2 per cent in the first month, to 61.1 per cent in the fourth month with an average of approximately 74.4 per cent whereas in the last 5 months of gestation the risk ranges from 11.1 per cent to 29.2 per cent, with an average of approximately 22.8 per cent. On this basis the claim by Swan and Tostevin[11] that every woman suffering from German measles during the first 4 months of pregnancy should be submitted to therapeutic abortion appears to be entirely justified. To judge by the interpretation of the law in the case of Rex *v* Bourne,[81] there would be no legal bar, for obviously if a mother knew that as a result of her contracting rubella at some stage during the first 4 months of gestation there was a 3 to 1 chance of her giving birth to a congenitally malformed infant, there would be every likelihood of her becoming "a physical or mental wreck" unless pregnancy were terminated.

It is to be hoped, however, that the elaboration in the near future of methods of immunization against the disease will render such drastic procedures as the termination of gestation unnecessary.

Social Aspects.

If large numbers of cases of rubella in pregnancy continue to occur they will constitute a social problem of some magnitude, for the consequences are not confined to the affected child. Indeed the shadow falls upon the family, especially the mother and the other children, on the children as yet unborn, and on the community generally.

The lot of children afflicted with a congenital abnormality of eye, ear or heart is a sad one, but when two or more of these defects are present in combination, and the more so if there is superadded mental retardation, their fate is tragic in the extreme and death at an early age can be only looked upon as a merciful release. Nevertheless, recent advances in cardiac surgery and in the perfection of deaf-aids offer real hope of the amelioration of these handicaps.

For the most part special schools for the education of the patients are necessary. In some instances, for example, in New South Wales, the provision of facilities for the teaching of more than 200 cases of deaf-mutism has had to be solved by the educational authorities. With regard to their education Swan and Tostevin[11] make the following statement:

"As far as is practicable, and especially so during the pre-school years, boarding-schools should be avoided, as children lose contact with other members of their

families, and return at holiday time to find themselves, as it were, 'strangers in their own homes.' Our aim should be to minimize rather than to accentuate the child's feeling of being 'different,' and to encourage him to take his normal place in society."

On the other hand, in instances in which the child is gravely handicapped a report of a statement by Gregg[82] concerning cases in New South Wales is apposite:

"So far the welfare of the child had been the main consideration; attention should also be given to the effect produced on the other members of the homes to which these children belonged. In many of the severe ocular cases the children were mentally deficient. There was no adequate provision for such children in New South Wales; only with difficulty could arrangements be made for their care after the age of three years. But by the time the child reached such an age, homes were disrupted. The mothers were asked to bear far too much. There should be some way of taking such a mentally defective child from the mother before she had to ruin her home, and her life looking after it."

Swan and his collaborators[12] found that approximately two-thirds of mothers who had borne a congenitally defective infant had not had any offspring subsequently. The authors believed that the mothers had refrained from having further babies because of the fear that these children likewise would be malformed. In order to combat the unnecessary limitation of families they advocated that wide publicity should be given to the fact that babies born of pregnancies subsequent to one in which rubella had occurred are free from congenital anomalies.

Contrary to expectation the publicity given to the effects of German measles in gestation has not caused undue alarm among the laity. Rather it has proved of benefit. Stimson,[83] for instance, refers to a woman who wrote to him after an article had appeared in the magazine *Time*. Once she had understood why her child had been afflicted with cataract and heart disease she was anxious to have further children; earlier she had refrained because she feared "that there was a family taint somewhere."

Conclusion.

The evidence adduced in the course of the present essay indicates beyond all reasonable doubt that a definite relation exists between the contraction of rubella in the early months of pregnancy and the occurrence of congenital defects in the infants born subsequently. Some critics have claimed that the association may be casual rather that causal. Against this claim, however, there are a number of strong objections. The first is the large number of cases—over 558—in which the relationship has been recorded. As Swan and Tostevin[11] have pointed out: "even more convincing is the fact that in these cases the period at which the mother suffered from German measles is virtually confined to the first four months of pregnancy, whereas if the association was fortuitous it would be reasonable to expect a more even distribution over each of the nine months." Finally, as another point in favour of the relationship, these investigators have drawn attention to the fact that the main ". . . malformations are reproductions of varying degrees of completeness of a specific syndrome, comprising cataract, deaf-mutism, heart disease and microcephaly."

It appears paradoxical that such a trivial disease as rubella should lead to such severe malformations and yet it is by the very nature of this paradox that the effects occur. It is now becoming clear that it is the relatively low virulence of the virus

of German measles which enables the embryo, though damaged, to survive. Unfortunately, however, although low virulence is accompanied by low mortality it also implies high morbidity, so that a mother who suffers during gestation from an infection of greater virulence than rubella and which is followed by death and extrusion of the embryo is in reality better off. A recent writer[74] has aptly termed the pathogenesis of the post-rubella syndrome "extrinsic sub-lethal interference with organogenesis."

Much work remains to be done. As far as rubella is concerned the most urgent need is an effective method of immunization. Attempts should be made to confirm the observations so far recorded by inoculating the virus into susceptible pregnant animals and noting the effect on the offspring born subsequently.

With regard to the part played by infectious diseases other than rubella in the production of congenital abnormalities, only the fringes of the subject have been touched.[9, 10, 11, 12, 20, 28, 29, 32, 35, 37, 54, 84, 85, 86, 87, 88] From their investigations Swan and his colleagues[12] stated that: "... there is little evidence as yet to suggest that morbilli leads to congenital abnormalities, though it is possible that it may be a cause of abortion. The question whether mumps and other virus conditions may be followed by congenital malformations remains open. As far as mumps is concerned, a number of defects have been recorded, but so far no definite syndrome, such as that associated with rubella has emerged. If other viruses are found to play a part in the aetiology of congenital anomalies, we postulate that they will be confined to those which circulate at some stage of the infection in the mother's blood stream."

The present position has been summed up by Ober and others[41] as follows: "A definitive study of the effects of rubella and other diseases during pregnancy on the resulting child has yet to be done. Such studies would involve finding cases while the mother is ill with the disease, verifying the diagnosis and the stage of pregnancy, following the pregnancy to its conclusion, obtaining careful autopsies on all infants lost by abortion or stillbirth, and following up infants to the age of 12 to 15 years, if necessary, to catch all important abnormalities. This type of investigation would be of considerable value, but would take a number of years to complete."

To facilitate such studies Swan[7] makes a plea for the compulsory notification of all infectious diseases contracted during pregnancy.

Despite the numerous investigations performed during the past few years, there are many aspects of the effects of contraction of infectious diseases during gestation which must, for the time being, remain uncertain. Nevertheless, the writer ventures to suggest that a stage has been reached when the words of Jaeger in reference to cerebrospinal meningitis are equally applicable to rubella. Jaeger wrote:

"The diffusion of this scourge appears to us now like a mountain range free from mist; only peaks without foundation are visible; yet we are perceiving now more and more the great bases upon which the peaks arise."

Summary.

On the available evidence, a woman who contracts rubella at some stage during the first 4 months of pregnancy, has a 3 to 1 chance of giving birth subsequently to a congenitally defective infant. After the fourth month the risk of congenital malformations is minimal. The type of abnormality is to some extent dependent on the time of onset of the infection. The main anomalies comprise cataract, deaf-mutism, cardiac disease and microcephaly; each

may occur alone or in any combination. The pathogenesis of the defects has been designated "extrinsic sublethal interferference with organogenesis." Termination of pregnancy is considered to be justifiable if a mother contracts German measles during the "critical period," i.e., the first 4 months of gestation. Methods of prevention of infection during pregnancy include quarantine, deliberate exposure to infection before the childbearing period, and the prophylactic use of convalescent serum and of gamma globulin.

Rubella in pregnancy may also play a role in the aetiology of intra-uterine death.

ADDENDUM.

Since the completion of the foregoing essay, new information has come to hand to which it is felt reference should be made here.

(1) *Active Immunization.*

Anderson[89] has shown that rubella can be transmitted at will to susceptible human beings by causing them to inhale atomized throat washings obtained at the height of the exanthem from patients suffering from the disease. The virus can be preserved in fully active state for at least 3 months in such washings by keeping them at the temperature of solid CO_2, so that a reliable and convenient source of immunizing agent is readily available. Unfortunately the infection evoked is communicable to others so that it would be necessary to isolate those subjects desirous of immunization. It is suggested that a holiday camp could be set up for this purpose, for the disease is usually so innocuous that it would be unlikely to interfere materially with normal holiday pursuits and activities.

(2) *Passive Immunization.*

In contrast to the experience of Aycock and Ingalls[32] using standard gamma globulin, McLorinan[90] has obtained encouraging results from the use of gamma globulin derived from the sera of patients convalescing from rubella. The globulin was injected in a dose of two cubic centimetres into women, the majority of whom were less than four months pregnant. Most of them were inoculated less than a week after contact with rubella.

(3) *Pathogenesis of the Congenital Malformations.*

Gillman and others[91] have stressed the fact that as yet there is no evidence in support of the hypothesis that the virus of rubella produces congenital defects by penetrating the chorionic or placental barrier and invading the embryo. On the basis of their investigations on trypan blue as a teratogenic agent in the rat, they suggest that the virus may induce a metabolic disorder in the mother which in turn may lead to congenital anomalies in the embryo.

In this regard it may be pointed out that, earlier, Swan and his co-workers[12] sought to prove that the post-rubella syndrome was the result of actual intra-uterine infection with the virus by showing that children suffering from the syndrome are immune to natural infection. In the follow-up study of 49 of the patients comprising their first and second series they found that 9 had suffered from whooping cough, 8 from morbilli, 8 from chickenpox and 2 from mumps. Only one child had contracted rubella and she was free from congenital defects. Nevertheless, although their data are suggestive, no definite conclusions can be drawn from them, because the children were relatively young and may not have come in contact with rubella despite the fact that some of them showed evidence of exposure to various other common infectious diseases of childhood. The crucial experiment would be to demonstrate that children congenitally malformed as the result of maternal rubella in pregnancy and

not having suffered from a postnatal natural infection, are immune to the disease induced according to the technique of Anderson.[89] The procedure might also prove of value in elucidating the pathogenesis in cases of maternal rubella in gestation which fail to lead to congenital abnormalities.

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