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Relationship of fetal abnormalities to maternal virus infection

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RELATIONSHIP OF FETAL ABNORMALITIES TO MATERNAL VIRUS INFECTION

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INTRODUCTION

In ancient times the birth of a deformed baby was commonly believed to be an omen, a supernatural judgment or the work of the devil. Old attitudes were gradually discarded and, with an increased understanding and application of Mendelian laws, anomalies present at birth were commonly intrepreted as a manifestation of genetically defective germ plasm.

Yet it had been known that fetal disease derived from the maternal tissue was a transmitted infection. The transmission of variola in this way first established by Duttel (25) in 1702 and Ballantyne (8) in 1902 referred to the transmission from the mother to the fetus of varicella, erysipelas, scarlet fever, measles and parotitis. A succession of events during the past ten years, initiated by observations in 1941 on the role of a virus as a cause of congenital malformation, has brought appreciation of the fact that congenital anomalies may be acquired as well as inherited.

When a congenital defect is due to factors which are not genetic in origin, offspring conceived subsequently should be congenitally malformed only with the same frequency as is commonly observed in the population at large. The chance of having defective children is

given as 47 per 10,000 live births in the general population (75). When an unusual number of cases of congenital cataract, observed in Sydney, Australia in the early months of 1941, continued to appear in numbers indicative of no chance phenomenon, serious thought was given to their causation. Their almost epidemic occurrence, their opthalmologic character, and their association with congenital heart disease suggested to Gregg (44) that the etiology was a constitutional, toxic or infectious disturbance in the fetus rather than a purely developmental defect. Calculations relating to the origin of congenital anomalies showed that an early stage of pregnancy coincided with the period of maximum intensity of a widespread epidemic of rubella. Gregg collected 78 instances of congenital defects, for which the basis was found to lie in maternal rubella during pregnancy.

The findings in the case of rubella were of great importance, not only because they furnish us with a definite causative factor for certain congenital anomalies, but also because they prove so well that congenital defects may be the result of maternal disease acquired after conception has taken place. Following Gregg's paper, physicans questioned that a disease previously considered so mild should produce such devestating effects in the fetus. Considerable discussion was stimulated and many

cases were reported, especially in the United States, and it soon became evident that the disease was actually rubella. Other virus infections of the mother leading to abnormal offspring were also observed.

Kock (65) has shown us that the fetus may become infected in utero via the placenta and that the placenta can be penetrated by all pathogenic microorganisms. Some of the more significant work on this subject has been done by Warkany (101) who demonstrated that numerous congenital malformations in the offspring could be produced by selective malnutrition of animal mothers in the period corresponding to the first eight weeks of human pregnancy. The eitiology of congenital malformations has been classified as due to defects in the genes or to nutritional, chemical, endocrine, actinic, mechanical and infectious factors (46). This last type, restricted to virus origin, is the subject to be discussed. Consideration will be given to the various effects of an attack of maternal virus during gestation, the nature and frequency of the sequelae, their pathogenesis, and the means of prevention.

VIRUS AND CONGENITAL ANOMALIES: OBSERVATIONS AND INVESTIGATIONS

Rubella

Rubella during pregnancy was early incriminated as a cause of fetal malformations. The majority of the investigations of abnormalities due to virus infection have been on the effects of German measles.

In 1941 Gregg(44) in Sydney recorded a series of 78 cases of congenital cataract; in 44 of them a congenital lesion of the heart also was detected. With the exception of 10 cases, a history of maternal rubella was present. The infection occurred in 67 of the mothers in the first three months of pregnancy and in one of them three months prior to conception.

Swan (97) and co-workers in 1943 gathered data from physicans in Australia to obtain information about children born to mothers who had suffered from an exanthema during pregnancy. Forty-nine of the mothers had suffered from rubella during pregnancy, 9 from morbilli and 2 from mumps. Of 61 infants examined, 36 were found with congenital defects. Rubella infected mothers gave birth to 31 infants with congenital defects including cataracts, deaf-mutism, heart disease, microcephaly and mental retardation. Eye defects in 14 cases included cataract, 13 (10 bilateral and 3 unilateral); buphthalmos, 1; deaf-mutism, 7; and car-

diac abnormalities, 17. All evidenced microcephaly.

Gregg (45) 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; deaf-mutism, 4; dental defects, 6; mental deficiency, 2; and mongolism, buphthalmos and strabismus, each one case.

In Australia, Evans (27) found 23 of 34 babies whose mothers suffered from German measles during pregnancy had congenital dental defects. These were most severe in those babies whose mothers had contracted the disease in the sixth to ninth week of pregnancy -- the critical period for dental development.

The first American observations were by Reese (85) who described 3 cases in 1944. All had suffered from rubella during the first month of pregnancy. The defects included cataract, 3 cases (2 bilateral, 1 unilateral); cardiac disease, 3; and microcephaly, pyloric stenosis and umbilical hernia, one case each.

Erickson (26) reported 11 cases from California in which the mother had contracted rubella in the first month of pregnancy, 1 in the second and 1 in the third month. All the babies exhibited defects including cataract, 9

cases (7 bilateral, 2 unilateral); microphthalmia, 1; unilateral corneal opacity, 1; cardiac disease, 9; and mental retardation, 2 instances. The heart defects were believed due to a patent interventricular septal defect. In no case was there a family history of congenital eye or cardiac anomalies.

Simpson (89) recorded the first cases in England in 1944. Two babies were born with congenital cataract and cardiac disease of mothers who had contracted rubella in the second and third months of gestation.

Carruthers (18) reported 18 cases of deaf-mutism in which the mothers suffered from rubella -- 2 in the first month, 10 in the second, 4 in the third and 1 in the fourth. Additional anomalies included stunting of growth in 12 instances, microcephaly in 3, and cardiac disease and strabismus each in one case.

In this country, Conte, McCammon, and Christie (22) in 1945 surveyed congenital anomalies and noted a history of maternal rubella in 4.2%. This figure exceeds by at least ten times the actual case rate of maternal rubella for the child-bearing age group in the population at large.

In the same year, a Committee appointed by the Director-General of Public Health of New South Wales (76) studied 136 cases of maternal rubella in the state. There were 130 instances of congenital defects. Maternal infec-

tion occurred in the first month in 13 cases; second, 50; third, 41; and fourth, 18; while the onset was indeterminate in 8 cases. Malformations included deaf-mutism, 111 instances; cardiac disease, 38; cataract, 22 (15 bilateral, 7 unilateral); and bilateral buphthalmos, 1 case.

Five instances of maternal rubella, 4 in the second and 1 in the first month, were recorded by Krause (66). Congenital abnormalities were cataract, 5 cases (3 bilateral, 1 unilateral); cardiac disease, 3; cerebral agenesis with mental retardation, 2; and 1 case each of mental retardation, deaf-mutism, spina bifida and dental aplasia.

Albaugh (4) described 7 similar cases, 3 instances occurring in the first month, 2 in the second and 2 in the third. The congenital defects consisted of bilateral cataract, 6 cases; cardiac disease, 6; microcephaly, 5; umbilical hernia, 2 and one each of pyloric stenosis and cryptorchidism.

Long and Danielson (72) describe 6 cases, 4 mothers being affected in the first month and the remainder in the second. Anomalies noted were cataract, 6 cases (3 bilateral, 3 unilateral); cardiac disease, 6; and bilateral cryptorchidism, talipes valgus, penile hypospadias, bilateral dacryostenosis, and strabismus each in one case.

In 1945, Martin (74) by questionaire found that in

36 cases of congenital deafness there was a history of maternal German measles at some stage during the first four months. Many of the children also had ocular and cardiac abnormalities.

Six cases were followed by Goar and Potts (38). Three mothers were affected in the first month, 2 in the second and 1 in the third. All of the infants had cataract (5 bilateral, 1 unilateral); heart disease was noted in 6, deafness and mental retardation in 1 instance each.

The same number of cases were studied by Aycock and Ingalls (7). Rubella in pregnancy occurred once in the first month and the remainder in the second. Anomalies were cardiac disease, 3; deafness, 2; mental retardation, 2; and cleft palate and cataract, each in 1 case.

Congenital deaf-mutism following maternal German measles in 11 cases were investigated by Hopkins (55). Two infections occurred in the first month, 3 in the second, 3 in the fourth, 2 in the sixth month and the time of the remaining case not accurately ascertained. Other defects encountered included cardiac disease, 4 cases; strabismus, 3; mental retardation, 6; and blindness, cataract and poor muscular coordination in one instance each.

Five cases of congenital heart disease influenced by

rubella were reported by Dogramaci and Green (23). Two infections were in the first month, 3 in the second. Additional abnormalities included cataract, 4 (3 bilateral, 1 unilateral); 1 instance of cleft palate, and 1 of malformation of the right fourth rib.

Ober (78) in 1947 recorded a New York State Department of Health Report in which women between 17 and 49 who might have been pregnant at the time their case of rubella was reported were sent questionnaires. Letters also were sent to the respective physicians for individual case reports. Infants with abnormalities were observed in 8 cases and abortions and stillbirths occurred in 9. Eleven of 17 abnormal pregnancies were in women who contracted rubella during the first trimester. Eight of 9 women reported by physicians had contracted rubella in the first trimester and only 3 normal infants resulted from these 9 pregnancies.

In schools for the deaf in the Manchester area in England, inquiries were made by Clayton and Jones (20) as to the number of children whose mothers had German measles during pregnancy. In 11.3% of 97 children with congenital deafness, a maternal history of the disease in the first four months of pregnancy was obtained.

In Sweden Hagstromer (48) observed a premature child with congenital heart disease, complete deafness and mental

retardation whose mother had a history of rubella at about the sixth month of pregnancy.

In 1948 in Australia, Swan (94) collected information by questionnaire from 760 women who had had 764 stillborn children. In 16 cases the mother had suffered from rubella; in 13 the attack was in the first four months. Rubella was the commonest of all the infectious diseases suffered except influenza.

Buffington (16) reported on two infants suffering from bilateral congenital cataracts following maternal rubella in the fifth and seventh week of pregnancy respectively. The second baby also showed a heart defect and a thryoglossal duct cyst.

In 1948, Patrick (81) reported on a rubella epidemic which occurred in Queensland in 1941. Data was available on 7,822 of the 21,589 births in that year and showed that rubella occurred during 262 of these pregnancies, one-half in the rural districts and one-half in Brisbane. The latter group was examined and it was found that about 40% showed cataracts, or auditory, cardiac or mental defects. A group of pregnancies with rubella resulted in almost 50% of the congenital defects while a control group of 1,000 pregnancies in the same year caused only 2%.

In Denmark Bardram and Braendstrup (10) listed the

case histories of 8 children whose mothers had rubella between the second week and third month of pregnancy. One was stillborn and one died at six months. Defects observed were cataracts, 7 (5 bilateral, 2 unilateral); microphthalmos, 3; buphthalmos, 1; pigmentary degeneration of the retina, 3; and incomplete iris coloboma, 1.

In the Netherlands, seven cases were described of congenital cataract, heart defects, deafness and mental and physical backwardness due to a maternal rubella infection (36). One survey (37) in an institution for the deaf and dumb children in Rotterdam found 59 children in whom deaf-mutism apparently was due to neither familial nor acquired affections. Four were recorded whose mothers had contracted German measles during the first month of pregnancy. A later survey (63) showed 135 cases of unexplained etiology. Of these, 14 had a history of maternal rubella during pregnancy.

In Switzerland, Hottinger (57) described a case of a three-year-old boy whose mother had rubella when two months pregnant. The child, followed for over a year, showed congenital cataract of the right eye and a congenital heart defect without cyanosis.

In 1948 in Sweden Zewi (108) described two children whose mothers had German measles in the first and second months of pregnancy respectively. The first showed bilat-

eral congenital hydrophthalmos and the second bilateral congenital cataract with microthalmis. Both were slow in physical and mental development.

In America in 1949 Hopkins (56) studied a group of 92 cases in which the mother had rubella during the first trimester of pregnancy and produced a deaf child. In 39 of these, other congenital defects included 10 cataracts and 30 cardiac anomalies.

Bewick and co-workers (14) made a study of 15 cases covering from 1944 to 1948. In all cases the mother had rubella during the first trimester. None of the children had congenital heart disease or cataract; the most consistent defect was deafness. They also described a case of congenital deafness occurring in 1936 in which the mother had rubella during pregnancy.

In a survey made by Abel and Van Dellen (1) in Chicago in 1949 82 letters concerning 84 infants were used. The letters were in answer to a request made through a syndicated health column in a newspaper. In this series, 3 children were stillborn, 25 were normal and 56 were abnormal. The principal anomalies were congenital heart disease, 19; cataracts, 17; deafness, 14; and mental deficiency, 7. There were defects in 87% of the pregnancies where rubella was observed during the first month of pregnancy; 42% of the babies were affected in the second month;

and no abnormal infants were noted due to infection in the third month. While there are errors in this method and the authors admit it, there is noted a high correlation between maternal rubella and fetal defects.

In Italy, Franceschetti (31) observed malformations in five infants whose mothers had suffered from rubella during pregnancy -- 4 had cataracts and one had pseudo-retinitis pigmentoso.

A double cataract, mental deficiency and serious motor defects were reported in an infant born in Mexico. Few cases have been observed in that country. The mother had lived on an isolated coffee plantation and contacted rubella while on a short visit to the capital, thus establishing the direct etiology, according to Alarcon (3).

Hay (53) observed 240 children in the School for the Deaf in New Zealand. One hundred were found to have a history of maternal rubella occurring from the second to the twenty-second week of pregnancy, usually in the second month. Fifty-eight per cent of the children had a high percentage of other congenital anomalies. Most were of average intelligence and seemed to possess some residual hearing ability.

Of 42 Tasmanian children with congenital deafness born in the years between 1938-1941 observed, Hiller (54) held rubella responsible for the condition in 32. Retinitis

was present in 5 cases.

In 1950 in Australia the following was noted by Anderson (5): 44 pregnancies with rubella infection in the first trimester showed 22 defective fetuses; 22 pregnancies with rubella infection in the second trimester only 3 showed defective fetuses; and of 14 pregnant women affected in the third trimester there were two abnormal children. In the first group heart lesions were present in 10 cases, cataract in 6, abortion in 4, stillbirth in 3, microcephaly in 3, and one case each of deafness, mental retardation, hypospadias and hydrocephalus.

A committee appointed by the National Association for the Prevention of Blindness and the American Academy of Pediatricans published a report (2) on results obtained by a questionnaire sent to 6,000 physicians in the United States who were listed as members of the specialty boards of Obstetrics and Gynecology, Ophthalmology, Otolaryngology and Pediatrics. They also sent an abbreviated questionnaire to every physician in the State of Kansas. Their finding brought out the significant fact that rubella often appears in epidemic form in the spring of the year and that the majority of t he defective babies are born in the fall, thus showing a relationship between acquiring the disease and fetal damage. The committee reported that of 199 mothers who had rubella in pregnancy there were 32 normal

infants and 167 with defects. In an analysis of statistics it appeared that about 5% of the congenital anomalies may be attributed to maternal rubella infection.

Rubeola

There is no lack of reports indicating that maternal measles during pregnancy may influence the child in utero. Duttel (25) in 1702 was aware of the transmission of measles across the placenta, and in 1800 Wilson (107) mentions that the fetus may "receive the measles from the mother". In 1902 Ballantyne (8) collected some twenty cases of congenital measles from the literature.

There is general agreement that the fetal disease was in much the same stage as the maternal indicating that the mother and child were probably both invaded by the virus at about the same time. Of interest is one of Ballantyne's (8) cases in which a mother suffering from measles aborted during the sixth month of pregnancy and the fetus showed a typical measles rash indicating that the placenta may be permeable to the virus at least as early as the sixth month.

Maternal morbilli may bring about a termination of pregnancy although reports differ on the frequency with which this may occur. Lynch (73) believed that the fetus rarely lived. Greenhill (43) in his review reported an abortion rate of 45% to 76%. Swan (96) reported 18 cases

of maternal measles during pregnancy with only one abortion. Chapple (19) says that measles in the first trimester of pregnancy "quite frequently" results in fetal death and subsequent abortion. Seldom, if ever, does he believe that there are any resulting malformations.

Stillbirth in association with measles during gestation seems most infrequent and only one case was found (94).

Cases of congenital defects in association with maternal morbilli are few and all have been reported since Gregg's discovery of the teratogenic action of rubella. Rones (86) reported such a case following maternal measles in the first trimester. Albaugh (4) noted two cases in each of which a congenital heart lesion, bilateral cataract and general slowing of development were present; one mother suffered from measles during the eighth week of pregnancy and the other was exposed during the fourth week. Swan (96) in 18 cases of maternal disease found that three of the offspring had congenital defects (heart disease, heart disease with pyloric stenosis, genu valgum).

Dogramaci and Green (23) reported obstruction of the right lacrimal duct in the offspring of a mother who had a mild infection during the third month of pregnancy. Gronvall and Selander (47) also reported a case of congenital defects associated with maternal morbilli during the first trimester. Fox and co-workers (30) in 1948

recorded a case of hare-lip, the mother having suffered from measles during the fourth month of pregnancy.

Hagstromer (49), 1948, observed congenital malformations (cheila-palatoschiasis in 1 case and palatoschisis, micrognathia and a rudimentary ear in the other) in two children whose mothers had been exposed to measles in the second month of pregnancy without showing any signs of the disease. The women themselves had had measles in childhood.

Bammatter and co-workers (9) presented a case in 1949 of microcephalus, deafness and talipes valgus in a one year old girl due to measles contracted by the mother at the onset of pregnancy.

Thus there are recorded in the literature 12 cases of congenital abnormalities associated with maternal measles (exposure only to this disease in 3 instances) during the first trimester. Obviously with so few cases coincidence cannot be excluded.

There are also recorded (96) 5 cases in which normal babies were born to mothers who suffered from measles during the first three months of pregnancy.

Smallpox

Smallpox may be acquired by unborn children. What happens will depend on the stage of pregnancy. In the

first few months it is almost certain to result in abortion (58). Bass (12) lists this as high as 50% to 60% of the cases.

Hoyne (58) observed one baby born at term on the eighth day of the mother's eruption and the child did not develop smallpox.

Schick (88) has call attention to an interesting fact concerning smallpox. Over 40 cases are known where an immune mother, who has had smallpox earlier in life, is exposed to the disease while pregnant and her offspring acquires the disease in utero. Schick explains this on the ground that the mother's immunity is cellular rather than humoral and that the antibodies are unable to be transmitted to the fetus. In countries where there is smallpox, pregnant women know that they should avoid contact with cases even though they themselves are immune.

In this connection it is interesting to note that vaccination of the pregnant mother is apparently harmless for the fetus. Greenberg and co-workers (42) found that there was no difference in the number of babies born with congenital malformations to women who were vaccinated than to those who were not vaccinated. Bellows, Hyman and Merritt (13) also made a careful statistical study of this when five million persons were vaccinated against smallpox in New York City in 1947. There were no more fetal defects in the women vaccinated during early pregnancy than in con-

trols and it was shown that smallpox vaccination during pregnancy did not increase the incidence of congenital malformation, stillbirths, abortions or infant deaths.

Poliomyelitis

In 1941 Kleinberg and Horwitz (64) made a study of women previously paralyzed by acute poliomyelitis and their obstetrical histories. A review of 29 such cases showed that a normal child was obtained in 24 instances (82.8%). The causes of stillbirth and of early fetal death which were recorded in 4 cases were associated with prematurity. Their belief is that, notwithstanding severe paralysis involving the abdominal and extremity muscles and occurring during gestation, a normal course of pregnancy and normal offspring may be anticipated.

Harmon and Hoyne (52) also stated that pregnancy had little, if any influence on the course of poliomyelitis in a paralyzed mother and, conversely, that in utero infection of the fetus occurs with rarity, if at all. This is because the virus is rarely found in the circulating blood stream.

An experiment is cited: a pregnant woman had bulbar poliomyelitis and the fetus died of asphysixa. The fetal spinal cord was inoculated into monkeys but no virus could be demonstrated. While this is not positive proof that the virus was not present, it might be interpreted in that way.

Aycock (7), in a study of poliomyelitis in pregnancy, collected 264 cases. Where the mother died of the disease with the fetus in utero are not included. Pregnancy terminated or resulted in a dead fetus in the two cases in the first month, in the majority of cases in the second month, and in five of the ten cases in the third month. Thereafter the outcome was, as a rule, a normal child if the report "normal delivery" can be so interpreted. In 3 instances (second, third and seventh months) there were defects in the infants while in 3 others (ninth month) the infant was reported to have suffered from poliomyelitis. His evidence suggested that the risk to the fetus in maternal polio is, as in German measles, high if the disease occurs in the first three months of pregnancy and less in later months. It is not clear, however, to what extent the hazard to the fetus may be the result of paralysis of the mother.

Many authorities continued to believe that poliomyelitis does not seem to affect the fetus. Diaplacental infection of the fetus with the virus was assumed to be impossible as the virus was assumed to be exclusively neurotrophic. In 20 cases of pregnant women with poliomyelitis, gathered from the literature by Kreibich and Wolf (67), no clinical symptom of the disease was seen in a living child nor could histological evidence be

found in the dead children. Yet they were inclined to the belief that hematogenic dissemination was possible. They gave a case history of a pregnant woman who gave birth to a child almost at term three weeks after being affected with poliomyelitis. The child had repeated attacks of asphyxia, marked flaccidity of the extremities and died 12 hours after birth. Investigation of the spinal cord revealed changes such as to lead to the conclusion that the child had been affected with poliomyelitis before birth via the blood stream.

Fox and co-workers state (30) that in poliomyelitis the over-all incidence for anomalies is about twice the expected rate and in case of poliomyelitis in the first four months of pregnancy, it is nine times the normal rate.

Other virus infections

In a small series (96) non-ocular abnormalities were found in babies whoe mothers had varicella, herpes zoster, scarlet fever and "influenza" during pregnancy. And after studying the effects of rubella in mothers on the fetus, Wesselhoeft (105) believed that other diseases as measles, chicken pox, herpes zoster and influenza might cause similar defects though less often than rubella.

Dogramachi and Green (23) in 1947 reviewed the charts

of 1,387 women patients who had suffered from a virus or exanthematous disease. There were six pregnant women who were affected for a period of four and one-half months or less. One had mumps and 4 scarlet fever. The infants were all well and apparently free from heart defects. Charts were examined of 434 children with congenital heart disease in which an adequate account of maternal health was recorded. Nine mothers had virus infection in the first 3 months of pregnancy -- 1 with poliomyelitis, five with rubella, 2 with influenza and 1 mother was exposed to rubella.

In Sweden it was found (47) that among 34 women who contracted mumps during pregnancy, 1 miscarried, 5 children showed malformations and the rest were normal. After epidemic hepitis (21 cases), 2 women miscarried and there were 4 premature births and 1 child malformed. The proportion of previous virus infections in the mothers of malformed children was investigated. Of 354 mothers of such children, 5 were found to have had mumps, 3 epidemic hepitis, and 1 chicken pox.

Yet in America, Swartz (98) observed that in 1947-1948 there were many cases of mumps in Chattanooga, Tennessee and 9 women were followed up who acquired the disease during pregnancy (2 in the first month, 1 in the second, 2 in the third, 2 in the fourth, 1 in the ninth and 1

during labor). None of the infants were born with congenital defects and all did well.

Twenty-three women who contracted varicella by the eighth week of pregnancy were followed by Laforet and Lynch (68). Their children showed multiple congenital defects including unilateral talipes equinovarus, underdeveloped lower right leg with paralysis and muscular atrophy of the leg, defective development of the toes, cortical atrophy, hypoplasia or aplasia of the cerebellum, internal hydrocephalus, bilateral optic atrophy, pilonidal sinus, torticollis to the right, cicatrical lesions of the skin of the lower extremity, undescended left testicle, and insufficiency of the anal and vesical sphincters.

One case of microphthalmos was reported in an infant whose mother suffered from chicken pox during pregnancy (99).

Garavias (34) recently discussed a mother 8½ months pregnant who developed chicken pox. Two weeks later she was delivered by caesarian for other reasons. The child showed a typical eruption of chicken pox and had an extraordinary mild infection, whereas the mother had been much more severely infected.

Maternal influenza may result in a dead fetus in which typical lesions of influenza may be found. Fetal mortality was given as 66% in 21 cases of maternal influenza (103).

Rabies have been inoculated into dogs from the brain of a fetus whose mother had died of the disease. The injected animals developed rabies (12). No malformations in living babies have been noted.

INCIDENCE OF FETAL MALFORMATIONS

The incidence of fetal abnormalities following virus infection is of major importance to the practitioner since every pregnant woman who has become infected wants to know what her chances are of having a normal child. When Gregg (44) and Swan (97) published their papers they concluded that if the maternal rubella infection occurred in the first weeks, the defective offspring might be as high as 100% and if in the first trimester, at least 50%. Yet these statistics could be in error since much of the data was obtained by collecting and tabulating information on a large number of defective infants.

Hay (53) observed 11 cases following rubella and 9 after measles during pregnancy without abnormalities in the newborn. However, Ramon (84) described 5 children with cardiac and ocular abnormalities. In none of these cases was there any evidence of maternal rubella during pregnancy.

In an analysis of 2,200 cases of rubella in Milwaukee in the years 1942-1944, Fox and Bortin (29)

interviewed 152 women of whom 11 were pregnant when they had rubella. Only one had a defective baby. Ingalls (59) in Boston made a similar survey and found about 25% of the women who had rubella in the first trimester gave birth to infants with abnormalities. Levinson (71) recently reviewed 724 congenital anomalies occurring in the past eight years attributed to rubella in the mothers. It was pointed out that in the same period only 115 normal children were born under similar circumstances. He considers the danger of rubella great in the first trimester, especially in the first month when up to 80% of such births resulted in defective children.

RELATION OF TIME OF MATERNAL INFECTION AND OCCURRENCE OF CONGENITAL MALFORMATIONS

One of the most perplexing questions concerning the virus problem is the one dealing with the regularity with which fetal defects follow maternal disease. There is no longer any doubt that they may cause fetal malformation but there is no unanimity of opinion as to the frequency of their occurrence. It is generally agreed that the earlier in pregnancy the mother is taken ill, the greater is the chance that the infant will be defective and that the first trimester is the most

dangerous period. There are reports of instances of defects following infections occurring late in pregnancy but the chance of transmission is greatly diminished at that time.

The first study which represents an adequate attempt to determine the numerical probability of congenital anomalies following rubella during pregnancy is that of Fox and Bortin (29). They found that of 152 married women who contracted rubella during 1942, 1943 and 1944, 11 had rubella during pregnancy -- 5 during the first 2 months, 4 during the second to the fourth month, one in the seventh, and one in the ninth month. They found only 1 of 11 cases of rubella in the first month in which pathology could be found.

Aycock and Ingalls (7) investigated 1300 cases reported to the Boards of Health of 2 Massachusetts communities for instances of rubella in pregnancy and found 4 cases -- two mothers affected in the second month, one in the fourth, and one in the ninth month. All babies were normal except one with mental retardation whose mother was exposed in the second month.

In Switzerland, Lefebure and Merlen (69) made a study of 2,247 cases with reference to the course of pregnancy and the effect on the fetus of rubella and other infectious or toxic factors. Among 2,153 cases

with normal pregnancy were 32 in which the child showed malformation. In 20 of these cases the infection had been contracted in the first three months of pregnancy and in all the children showed malformations. In 14 cases in which the mother suffered an incurrent illness at a later stage of pregnancy, all of the children were normal.

Gordon and Ingalls (41) consider congenital cataract and certain types of congenital heart defects to be associated with infections developed in the first trimester of pregnancy. At this period, they believe rubella may result in the death of the fetus, in some specific developmental defect or in no manifest abnormality.

In Table I (next page) is shown a summary of 206 cases of congenital malformations due to rubella. The majority of the malformations affect the eyes, ears, heart or brain. Ninty-eight and six tenths per cent of the infections occurred in the first four months with the greatest incidence (40.8%) occurring in the second month. No infections involving abnormalities were noted in the last trimester of pregnancy.

In a small series on measles (Table II), the second month again had the highest incidence of infection.

Similar results on fewer cases were found in the virus infections previously discussed. Smallpox in the

TABLE I.

Time of Maternal Rubella Infections Involving Fetal Abnormalities

Investigator	No. Cases	Month Affected									Organs Affected
		1	2	3	4	5	6	7	8	9	
45	10	6	3	1							Eye, heart, ear, teeth
26	13	11	1	1							Eye, heart, brain
89	2		1	1							Eye, heart, brain
76	122	13	50	41	18						Eye, heart, ear
18	18	2	10	4	1		1				Eye, heart, ear
66	5	1	4								Eye, heart, brain
4	6	3	2	1							Eye, heart, brain, ear
72	6	4	2								Eye, heart, sex organs
38	6	3	2	1							Eye, heart, brain, ear
7	6	1	5								Heart, brain, ear
56	10	2	3	3			2				Heart, brain, eye
108	2	1	1								Eye, brain
Total	206	47	84	53	19	0	3	0	0	0	
Per Cent	100	22.8	40.8	25.8	9.2		1.4				

TABLE II.

Time of Maternal Rubeola Infections Involving Fetal Abnormalities

Investigator	No. Cases	Month Affected									Organs Affected
		1	2	3	4	5	6	7	8	9	
4	2	1	1								Eye, heart
23	1	1									Lacrymal duct
30	1			1							Hare-lip
49	(exposed) 2		2								Ear, skull
Total	6	2	3	1							

first trimester frequently resulted in abortion. Poliomyelitis in the same period may result in fetal defects. Parotitis and varicella have been involved in the etiology of fetal malformations if the infection were early in pregnancy.

The mean critical period for cataract is a 1.17 months and for deafness at 2.17 months of prenatal life in a series by Ingalls and Gordon (62). The determining factor for the malformations is that a single agent may give rise to multiple defects when acting at a specific stage of embryonic differentiation. It is interesting to check the embryological development at this time.

At three or four weeks the embryo is about 2 mm. in length and at this time a lens placode develops from the ectoderm which soon invaginates to form the lens vesicles. By five and one-half weeks (6 mm. embryo) the lens lies free from both the surface ectoderm and the optic cup which has formed from the neural tube. The inner cells of the lens vesicle increases in height and obliterated its cavity by seven weeks (17 mm. embryo) while the outer cells form the lens capsule.

The mammalian heart arises from two halves which secondarily unite. In an embryo of six weeks (10 mm.), the heart exhibits the general external shape and markings that characterize it permanently. The interventricular septum is formed at approximately seven weeks and it is about the last development to take place in the embryonic heart. The interauricular septum (foramen ovale) remains partially open until after birth (6).

In the ear formation, a placode invaginates to form the auditory pit at four weeks. Semicircular ducts start at the sixth week and the cochlea elongated and differentiated from the sixth to the eighth week. By the third month the organs of Corti become apparent along with the formation of the tectorial membrane and the membraneous labyrinth attains practically its adult configuration. From the third to the fifth month the entire cochlear duct undergoes expansion (82).

NATURE OF CONGENITAL DEFECTS AND PATHOLOGY INVOLVED

Maternal virus disease may be followed by an abortion, a stillbirth, a malformed infant, or even a normal infant. If the infant is carried to term, it may be born with one or more defects. Many of the children grow up mentally defective. Many suffer from more than one defect. In most cases the defects are multiple and may be spoken of as the "rubella syndrome" or"Gregg-Swan syndrome" in which the child is afflicted with cataract, heart malformation and mental retardation.

In a study of world literature (32) there were found 479 cases of malformations following maternal rubella infection. These included cataract, 273; deafness, 215; cardiac lesions, 181; microcephaly, 52.

The chief manifestations of rubella-embryopathy from a survey by Werthman (104) are given as cataract, heart defects and deafness. Particularly early and severe infections lead to abortion.

Refer to Table III (page 38) for results obtained by this author in his compilations from the literature.

Abortions, miscarriages and stillbirths

Wesselhoeft (106) has noted 31 cases of abortion in women who had rubella during pregnancy. Twenty-seven of

these occurred during the first four months of pregnancy. In Table III are listed 60 abortions and 13 stillbirths due to rubella. Abortion is most common with early measles infection while stillbirth is rare (93, 73, 43, 19). Smallpox has a similar effect (58, 11). Abortions have been noted in poliomyelitis (7) and fetal death shortly after birth (12). Miscarriage was found in women who contracted mumps and epidemic hepititis (47). Fetal mortality due to maternal influenza may be extremely high (103).

Eye defects

The special opthalmologic features were cataract, usually bilateral, and of a subtotal type often associated with nystagmus, strabismus and a sluggish pupillary reaction to light. There appear to be two types of cataract. One has a pearly central opacity about which lies a smoky area appearing less dense surrounded by a narrow peripheral ring of clear cortex through which a red reflex shows. The other is more uniform throughout. Often the cataracts progressively increase in size. Microphthalmos is frequently concomitant with cataract (26, 10). Gregg (44) noted it in approximately two-thirds of his monocular cases.

Atrophy of the iris may be seen (44, 66). Naso-lacrimal stenosis can be found (4, 72) along with buphthalmus (45); corneal opacity (26); and pigmentary degeneration

of the retina (10).

In 1947 Terry (99) noted the following changes in the eyes of a baby with bilateral cataract: the retinal ganglion cells appeared small, 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. The fetal nucleus of the lens almost touched the anterior pole of the lens, thus preventing the lens fibers from growing forward to insert themselves in front of the nucleus.

Deaf-mutism

Deaf-mutism has been reported by many investigators (18, 37, 56, 66, 95) with deafness alone more uncommon. Muteness when present was regarded as secondary to deafness. Swan and his co-workers (96) in 1946, in a re-survey of 49 out of 61 previously reported children with cataract, found four further cases of deaf-mutism. They believe that the association of deaf-mutism with cataract may be missed because the former is difficult to recognize under the age of two and the children with cataracts have a relatively high death rate.

Carruthers (18) examined the aural structures of an infant who died at the age of six months, with a maternal history of rubella infection in the first month. The

baby suffered from bilateral cataract, 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 eighth 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 organs of Corti. There was also lack of differentiation of the crista, the receptor end-organ.

While the character of deaf-mutism appears to be of the inner-ear type, it is not absolute and often the children are able to hear long, sharp noises and high pitched sounds. Swan and his associates (96) were of the impression that the high tones were better appreciated than the low tones, but the audiograms of Clayton-Jones(20) series do not confirm this view and show that the loss of hearing is usually fairly uniform throughout the frequency range. In audiograms of rubella deafened children, Hiller (54) found no one type of curve but showed an asymmetry between the audiograms of the two ears in a single case is common and may be extreme. The downward trend of the audiogram from low to high tones is usually not so steep as in the typical inner ear deafness. On examination the external canal and ear drums were normal.

Cardiac lesions

The common defects were patent ductus arteriosus (44, 85, 97) and patent interventricular septum (44, 56, 85) but one case of tetralogy and a possible example of a bicuspid aortic valve with regurgitation (56) were also noted.

Cardiac pathology was manifested by a harsh systolic murmur over the precordium usually loudest over the base of the heart or pulmonic areas and an absence of cyanosis (7).

In three postmortem examinations described by Swan (95), the ductus arteriosus was widely patent, there was variable patency of the foramen ovale, and one baby had an interventricular septal defect. 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 were occasional replacement of muscle fibers by connective tissue.

Microcephaly, mental deficiency and retardation

In a 13 month male, mentally and physically backward, autopsy findings (33) included microcephaly, generalized microgyria, agenesia of the corpus callosum, absence of the anterior commissure and hippocampal commissure and bilateral cataract. Microscopically, there

were remnants of fetal encephalitis with an increase of astrocytes and microglial cells in white mater, and meningeal infiltration with granulocytes, monocytes and very few neutrophils. In the cortex there appeared a slight paucity of nerve cells with complete absence of Betz cells and no pyramidal tracts. In the white matter there was a deficient myelination of nerve fibers with a partial disappearance of axis cylinders.

Mongolism

Swan and his co-workers (96) in 1946 believed that there was no ground for the belief that rubella could cause mongolism. But in 1947 Ingalls and Davies (61) made a study of the case histories of fifty mongols. They found 7 cases of intercurrent infectious disease (influenza, otitis, mastoiditis, rubella and parotitis) occurring during pregnancy. Six cases occurred after the first month and 1 case after the sixth month of gestation. Each pregnancy ended in the birth of a mongolian idiot. While this small series may not be significant,the tendency to localization of the particular maternal disease at a specific stage of pregnancy is provocative. It is held that mongolism may be produced by a variety of maternal injuries which result in deviations from normal development at about the eighth week of fetal development.

Miscellanous

Those due to rubella are listed under Table III. Similar findings are the results of other virus infections, except that measles and smallpox usually result in abortions. In addition, Dagramaci and Green (23) reported a case of harelip due to measles, and hydrocephalus, pilonidal sinus and torticollis related to varicella.

Evans (27) in 1944 examined 67 children, 30 of whom suffered from congenital dental abnormalities, in 20 cases major in degree (caries disregarded). With 5 exceptions all infants exhibited other congenital anomalies. The malformations were mainly confined to children whose mothers had contracted rubella during the first three months of pregnancy. The main abnormalities included retardation of eruption of the deciduous teeth and enamel hypoplasia. In a second series, Evans (28) found that of 34 babies whose mothers suffered during pregnancy from rubella, 23 exhibited congenital dental abnormalities; 18 cases were major in nature such as "sharklike" and "pointed" incisors and enamel hypoplasia.

Finally, it was noted that most of the babies were of small size, ill-nourished and difficult to feed. Swan (95) noted that the average birth-weight of 45 infants with congenital anomalies was 5 pounds,11 ounces

TABLE III.

Fetal Abnormalities Associated with

Maternal Rubella Infection

Abortions: 60 (5,7,29,78,94,106)

Stillbirths: 13 (5,10,78)

Ocular Malformations: 183
- 167 - Cataract (1,4,5,7,10,16,23,26,38,44,45,56,66, 72,85,95)
- 2 - Buphthalmus (44,95)
- 1 - Corneal opacity (26)
- 5 - Strabismus (18,55,72)
- 3 - Pigmentary degeneration of the retina (10)
- 1 - Pseudoretinitis pigmentosa (32)
- 4 - Macrophthalmia (10,26)

Ear Defects: 162
- 125 - Deafness (1,38,56,63)
- 37 - Deaf-mutism (18,56,66,95)

Heart Lesions: 139 (1,4,5,7,16,18,23,26,44,45,55,66,95)

Brain Damage: 70
- 49 - Microcephaly (4,5,18,85,95,97)
- 1 - Hydrocephalus (5)
- 20 - Mental deficiency (1,5,7,26,38,44,45,55,66)

Dental Defects: 30
- 29 - Enamel hypoplasia (27,44,55)
- 1 - Dental aplasia (55)

Miscellaneous: 32
- 13 - Physical retardation (18,56)
- 2 - Cleft palate (7,23)
- 1 - Thyroglossal duct cyst (16)
- 1 - Pyloric stenosis (21)
- 1 - Mongolism (41)
- 1 - Spina bifida (66)
- 2 - Umbilical hernia (4)
- 2 - Cryptorchidism (4,72)
- 3 - Penile hypospadias (5,31,72)
- 1 - Bilateral dacrostenosis (72)
- 1 - Displacement of 4th toe (66)
- 1 - Talipes valgus (72)
- 1 - Ovarian cyst (31)
- 1 - Ependymal pseudocyst (31)
- 1 - Pulmonary stenosis (21)

SUMMARY: 689 abortions, stillbirths and fetal malformations from 559 cases of maternal rubella infection described by 29 investigators between 1941 and 1951.

(2,580 gm.), whereas in 16 normal babies, whose mothers also suffered from rubella during gestation, it was 6 pounds, 12 3/4 ounces (3,083 gm.). Similarily in 18 babies with congenital malformations described by Carruthers the average birth-weight (18) was about 5 pounds, 14 ounces (2,665 gm.), in 34 recorded by Swan and Tostevin (97) it was 6 pounds, 2 1/2 ounces (2,793 gm.), in 130 reported by the New South Wales Committee (76) it was 5 pounds, 15 ounces (2,693 gm.) and in 12 investigated by Clayton-Jones (20) it was 5 pounds, 15 3/4 ounces (2,715 gm.).

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.

PATHOGENESIS

Experimental development of congenital malformations

Stockard (91) early demonstrated that exposure of a fish egg at about the fourteenth day after fertilization to weak solutions of chloroform, alcohol or magnesium sulfate generally result in cyclopia and later (92) showed that anesthetics may affect an animal fetus.

Warkany (101) stressed the fact that the same deformity may appear as a result of varied causes. For instance, cleft palate may be due to a genetic cause or

it may appear after exposure of the pregnant rat mothers to x-ray, or may appear if they have been placed on a riboflavin-free diet during pregnancy (102). Fetal defects or death in mice may result from anoxia (60).

Goodpasture (39) demonstrated the passage of vaccina through the placenta and gives evidence of his belief that the viruses of measles, smallpox and lymphocytic choriomeningitis can regularly pass through the placentas. With Anderson (40), he also grafted human amnion and chorion on the chorio-allantios of developing chick embryos and successfully infected these with the viruses of herpes simplex, variola and vaccina with typical lesions produced. These viruses grew readily on the amnion but the chorion was relatively difficult to infect.

Insulin (used as a noxious substance affecting developing fetal tissue) was injected into the yolks of developing hen's eggs and gave rise to a number of developmental abnormalities, including spina bifida, abnormalities of the limbs and beak, eye changes and certain skeletal defects which can be compared with osteogenesis imperfecta (24).

Another report on inoculation of hen's eggs, with the virus of Influenza A by Hamburger and Habel (51), states that varied defects could regularly be obtained.

Their conclusions were as follows:

"Experimental evidence has been presented to show that Influenza A virus has teratogenetic effects on the early chick embryo. It produces a specific syndrome, comprising microcephaly and microencephaly, twist of the axis, and impairment of growth of the amnion. The virus is lethal for early embryos within three days after infection. The mumps virus is also lethal for early embryos within five days after infection. It does not produce specific abnormalities but seems to raise the incidence of malformation of the types which occur occasionally in uninfected chick embryos. The patterns of infectiousness are different for the embryo and for the fully developed structures. In the embryo, the brain tissues seem to be particularly susceptible to Influenza A virus, whereas in the adult the respiratory mucous membranes are primarily affected. In mumps, the inflammation of the salivary glands is frequently combined with meningitis, but no effect on the brain was found macroscopically in embryos. The situation is the same as in rubella where the embryonic defects seem to have no obvious relations to the manifestaions of rubella infections in older phases of life."

An interesting series of experiments by Gillman, Gilbert and Gillman (35) was subcutaneously injecting female

rats with trypan blue before and after conception. It was assumed that the dye was absorbed by the plasma albumen with resulting changes in the plasma proteins which would cause changes in the chorionic villi that would be harmful to the embryo in the relatively anaerobic stage of blastocyte formation and of the formation of the ectoplacenta. The use of the dye could be appropriately manipulated to increase the incidence of malformed offspring to 80%. The authors cite what they consider to be an apparent parallel in the deviation of congenital defects in offspring of trypan blue-treated rats and the defects in infants following rubella infection. It was suggested that the supposed mode of action of the rubella virus on the human fetus be re-examined as they considered that passage of virus through the placental barrier was still considered debatable and as they demonstrated that the trypan blue in maternal rats did not enter the fetus, the amniotic epithelium or amniotic fluid. All embryonic tissues apart from the yolk sac were free from trypan blue particles.

Modern theories on viral effects on the fetus

The role of the placenta as a barrier between the mother and the fetus has long been a matter of dispute. It is now fairly well established that the intact placenta does not permit the passage of microorganisms but

this can occur when there is a pathological condition of the placenta. Particles smaller than bacteria are able to cross the barrier at any time. Immune bodies, as antitoxins, precipitins, bacteriolysins and antibodies occur regularly in the fetus. It has often been demonstrated that diphtheria antitoxin appears in the newborn infant in the same titer as it is present in the mother's blood. Incidently, it has been shown that the placenta becomes less permeable for maternal antibodies during the latter months of pregnancy (15). In fact, the fetus may even be affected by exposure to a viral disease to which the mother is immune (12).

The possibility of two strains of virus has been suggested (96) -- one with and one without an affinity for embryonic tissue. Or perhaps two clinically similar conditions, both called rubella. But after wide, thorough investigations these theories were discarded.

There is also the postulation that more severe virus infections, such as rubeola may kill the fetus, whereas the milder rubella merely damage the surviving fetus (96). However, this is not borne out by the findings of only three terminations of pregnancy in eighteen cases of maternal morbilli (79).

Parsons suggests (80) that in mammals the embryonic cells are more susceptible to virus infection than adult

tissue. More severe changes should be seen in the fetus and these should be especially marked at the period of greatest embryonic activity, i. e. the early weeks of pregnancy. Along this line, Sabin (87) has reported on the varied resistance offered to viruses. He showed that some viruses are neuro-tropic and that in the young animal they travel along a nerve to the central nervous system; in adults on the other hand a block develops in the nerve and prevents the virus from reaching the brain, thus producing encephalitis. However, if the virus is injected directly into the adult brain, encephalitis results. Further, if the virus is injected intraperitoneally, the young mouse develops encephalitis but the adult fails to do so. It is of interest to compare this with the action of the rubella virus which acts so differently on the mother and the fetus.

The influence of high rates of growth at given points may be effected by injurious agents. The defect produced is more severe in a part whose rate of growth is higher than those of others exposed to the same agent. Up to a certain limit, this may be compensated by a great ability of the rapidly growing part to make restitution of itself. Beyond that limit, the permanent damage will be greater in a part with a high growth rate than elsewhere (83).

Of great interest was the experiment discussed above

by Gillman and co-workers (35). On the basis of their results, the view is put forward that rubella and other infections of a woman before or after conception produce a general metabolic disturbance. In the case of this metabolic disorder coinciding with that stage of embryonic development when somites are differentiated and when chorionic villi establish contact with the maternal blood, malformations may appear in infants. Malformations following rubella infection during the last stage of pregnancy cannot be related to this infection but to some unrecognized metabolic disorder occurring either before conception or during the initial stage of pregnancy.

PREVENTION OF ANOMALIES

Antibodies reach the fetus freely through the placenta and offer an opportunity for influencing the fetus through the mother. Maternal infection and immunity can produce in the childbearing female an immunity to the common childhood diseases especially virus. It has been proposed to prescribe exposure of young girls to rubella whenever possible (58, 90) and even to chickenpox, measles, and mumps as well (90). Aycock (7) advocates females actually to seek exposure if they have not contracted the disease by adolescence.

In Australia, Burnett (17) was able to show that rubella infection of human volunteers could be induced by inhalation of atomized throat washings. He was able to obtain the virus found in high concentrations in throat washings taken at the height of the rash and was able to preserve it for three months at the temperature of solid carbon dioxide. When sprayed into the throats of susceptible young women, the disease could be acquired and transmitted to others by ordinary contact. The incubation time is 13-20 days and the immunity lasts longer than nine years (5).

Wesselhoeft (105) seriously questions if a child should be exposed deliberately since the infection does not always give a permanent immunity.

Not only should pregnant women avoid exposure to virus infection, but it is important that she should not attempt pregnancy for at least two months after exposure since maternal rubella even six weeks before conception has resulted in defective offspring (12).

Measures should be taken to protect women against infection in early pregnancy (70). Gilse (36) treated five pregnant women who had been in contact with rubella with 100 ml. each of convalescent serum and none developed the disease.

Another prophylactic therapy that can be offered an

exposed pregnant mother is immune globulin (7). This may be effective in the incubation period and should be tried (63, 93).

Gamma globulin has been found to be effective against measles and was tried as a prophylactic measure against rubella by the New York County Medical Society in 1948 (77). They found that the globulin may have been effective in preventing rubella, although it was not effective in every case. As yet, it is not known whether the prevention of symptoms in the mother has always protected the fetus (12).

The compulsory notification of health authorities of infectious diseases contracted during pregnancy has been advocated so that more serious efforts to meet this problem may be made(94).

What should be the procedure if, in spite of any preventive or prophylactic measures, the pregnant woman develops a virus disease? Many authorities debate the justification of therapeutic abortion. Others consider available evidence as sufficient grounds for the termination of pregnancy.

Gilse (36) rejects abortion when the infectious desease is rubella, and Smith (90) does not think the proof sufficient yet that chickenpox, measles or mumps justify an interruption of pregnancy. Filho and Cerruti

of Brazil (100), after a review of the literature, believe the danger is not as great as at first thought to be and conclude that when a woman in the first three months of pregnancy gets rubella, this does not mean that she must have a therapeutic abortion.

Yet others feel that the termination of pregnancy must be considered (12, 96). They aptly consider the birth of a defective infant who may also be blind and deaf as a frightful calamity. It is not only an unbearable burden for the parents, but the care of such a child consumes so much time and money that the normal children in the family are neglected. And many women are concerned and refrained from having further children due to the fear of having more malformed children.

Certainly, at the present moment, this matter may be regarded as debatable and is considered by many to be of individual case consideration with a consultation of a psychiatrist and obstetrical specialist a necessary step before final conclusions as to abortion can be reached in any single instance.

SUMMARY

The evidence adduced in the course of the present thesis indicates beyond all reasonable doubt that a definite relationship exists between the contraction of a virus disease in the early months of pregnancy and

the occurrence of congenital abnormalities in infants born subsequently.

Rubella has been implicated too many times in different countries to be considered more than a casual relationship. Those mothers who suffered from German measles, with resulting fetal abnormalities, were affected mainly in the first 4 months of pregnancy. If such occurrence were fortuitous, it would be reasonable to expect a more even distribution over each of the nine months. These defects, the "Rubella Syndrome", are variations of a syndrome which includes cataract, deaf-mutism, cardiac malformations, mental retardation, microcephaly and dental defects. In addition, the infants often are underweight at birth and are feeding problems.

Much less commonly, rubeola and smallpox have shown their effect to be abortion in early pregnancy. Poliomyelitis commonly results in no abnormalities in late pregnancy but in the first four months can result in abortion or fetal defects. A number of defects have been recorded in association with mumps but no definite syndrome has been observed. Varicella, infectious hepatitis, influenza and herpes zoster infrequently have been correlated with fetal abnormalities.

Thus, when a pregnant woman contacts an infectious viral disease there may be a number of possibilities (96):

1.)the fetus may be unaffected; 2.)as a result of the direct action of the noxia or the indirect action of the associated pyrexia, the fetus may die, and an abortion or stillbirth may result according to the stage of gestation; 3.)in early pregnancy the infection may lead to congenital abnormalities, such as ocular or cardiac defects, as well as exerting a general deleterious effect on the embryo. The damaged embryo may than (a) be unable to survive to term and an abortion may 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.

Rubella is the greatest problem to be met and here an effective method of immunization that may be widely used is the urgent need.

Much work remains to be done in evaluating the role of virus diseases on pregnancy. This might be done by the collection of statistics in large obstetrical hospitals over a period of many years, obtaining accurate prenatal histories, observing the mother during pregnancy, obtaining careful autopsies on all infants lost by abortion or stillbirth, and carefully examining the offspring for several years. To facilitate such studies the compulsory notification of all infectious diseases contracted during pregnancy should be instigated.

Despite numerous investigations performed during the past few years, there are many aspects of the effects of contraction of infectious virus diseases during gestation which must, for the time being, remain uncertain.

.CONCLUSIONS

On the available evidence, a woman who contracts a virus infection in the first four months of pregnancy has a 3 to 1 chance of giving birth to an infant with fetal malformations. The type of defect is associated with the time of onset of the infection. Rubella causes a syndrome including cataract, deaf-mutism, heart defects and microcephaly. Each may occur alone or in any combination; intra-uterine death may result. Less frequently, smallpox and rubeola may result in abortion. Parotitis, poliomyelitis, influenza, varicella, herpes zoster and infectious hepatitis result in defects without a definite syndrome in the first trimester of pregnancy.

Methods of prevention include vaccination, quarantine, deliberate exposure of girls before the childbearing age, avoidance of exposure while pregnant and avoidance of pregnancy two to three months after being infected. In exposed pregnant women, convalescent serum or gamma globulin is used prophylactically. Termination of pregnancy is considered justifiable if German measles is contracted in the first four months of pregnancy.

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