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Diagnosis of maternal rubella and the congenital rubella syndrome

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DIAGNOSIS OF MATERNAL RUBELLA AND THE CONGENITAL RUBELLA SYNDROME

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TABLE OF CONTENTS

Congenital rubella is a relatively new disease entity. Material is even now being gathered from the 1964 epidemic stated to be the largest outbreak in the continental United States in twenty years.[1] The total number of affected mothers and children is still not known [10], but has been estimated to be one million eight hundred thousand as of July, 1964. The long range effects may not be completely appreciated for decades to come. Many new tools have been utilized in the detection, diagnosis, and epidemiology of this most recent outbreak. Most of these either were not available or were in limited use with previous epidemics.

To understand the import of the newer knowledge over the past twenty years concerning rubella and rubella caused malformations, I will attempt to briefly retrace the events against which this newer knowledge has developed.

In the early part of the twentieth century there were few papers written, and little attention paid to this trivial exanthem. What few papers written were directed toward confirming again the classical eighteenth century German concept of rubella as a separate entity, and to differentiate this infection by clinical criteria from other exanthema, notably mild rubeola. As late as 1899, a Dr. Townsend of Boston[2], argued there was no basic difference between these two diseases.

During the first four decades of the twentieth century little of lasting consequence appears to have been published

about rubella. Nothing is to be found describing the adverse effects of rubella in the first trimester of pregnancy until World War II. In Australia a significant portion of the adult population must have been susceptible at that time, for sizeable epidemics in 1939 and 1940 developed in which many young women in the early stages of pregnancy contracted the disease. The stage was set for the appearance of the famous crop of "rubella babies", born in 1940 and 1941. The first clinical manifestation ever noted and thought to be linked in a causal manner was congenital cataracts reported by Gregg in 1941.[3] The usual partial deafness that was soon to be detected, and the frequently accompanying congenital heart disease and mental retardation were not so quickly discovered in early infancy as the dense, white opacities in the lens.

In 1946, Fox and Bortin[4] described the outcomes of nine rubella complicated pregnancies in the first trimester of pregnancy, one of which resulted in still birth and one in a "blue baby". Since then several other series have been similarly analyzed. Usually, the number of patients reported in any one series has not been large, and many deformities now detectable were not recognized at that time. In one review series[5], based on over 1,000 cases accumulated until 1961, the author shows incidents by trimester with both death and fetal deformity included. (See Table 1) This table shows that nearly one-third (30.7%) of pregnancies complicated by rubella in their first trimester are

in danger. Although not included separately in this table, the author further states that after German measles in the first two months of pregnancy between one third and one half of the mothers are either going to lose their child or give birth to a child with significant defect. A widely held misconception is that the second and third trimesters of pregnancy are not significantly influenced by rubella. It can be seen, however, in Table I that rubella infections in the second (6.8%) and third (5.3%) trimesters also are associated with significant death and deformity.

Even these figures are somewhat misleading. At this time there are many ways of investigating, reporting, and classifying these deformities. The criteria for detecting and determining maternal and fetal infections also vary widely. What one study group finds may very well be missed by another, simply due to these differences. Also, in no paper did I find any attempt to compare the reportedly rubella induced morbidity and mortality with the expected morbidity and mortality in pregnant women and their offspring in the population at large. Even at this time certain manifestations of the 1964 outbreak may not yet be apparent. For example, the risks of congenital deafness have been investigated by retrospective studies carried out in England by Jackson and Fisch.[6] They state that when German measles occurred between the ninth and fourteenth weeks of pregnancy, there was a 30% chance of detectable loss of hearing in the subsequently born

baby, if that child were followed and tested until the age of four. Thus, deafness may be nearly twice as common as previously reported, further indicating the need for repeated examinations and follow-up over a period of years.

The rubella epidemic in 1964 was first noticed on the east coast with peak incidence in March and April, and spread from there to the west and northwest by summer. Oregon reported maximum incidence in June, 1964, with intervening locations having separate specific peaks. The only completely reliable method of determining maternal infection is to have paired sera for antibody determinations.[7] In this study, three distinct study groups were examined, each with varying past histories of rubella infection. Sera for preexisting antibody determinations was then taken and the subjects allowed to resume their normal activities for a period of eight weeks with varying rates and length of exposure to known rubella infections. If any person became ill during this period, she was examined and serial throat cultures and blood for viral isolation were collected during the period of illness.

At the end of eight weeks all persons were then again studied for serum neutralizing antibody. Only a fourfold increase in antibody titer was considered significant. Of a clinic personnel group (C.P.G.) of 18 with median age of 36.2 years, 16 persons (88.9%) had pre-existing antibody, and none of these either had illness or antibody titer rise. Two people (11.1%) had no pre-existing antibody, no clinical illness, and no rise in titer after

eight weeks with adequate exposure. In a student nurse group of 64 patients, fifty three (82.8%) had detectable serum neutralizing antibody titer at the start of the study. They showed no clinical illness and no significant rise in antibody at eight weeks. Of the eleven students without neutralizing antibody at the start, rubella developed in six for an attack rate of 50% of those who lacked antibody, and 9.4% for the over-all group of 64. A housewife control group was also used with each household having two or more children with a diagnosis of rubella. All of these women had pre-existing antibody and none became ill or demonstrated rise in serum neutralizing antibody.

These results compare favorably with previous studies on experimental rubella which show that human volunteers with pre-existing neutralizing antibody were protected from subsequent viral challenge.[8] After the development of the rash, volunteers developed low levels of antibody, which after four weeks rose fourfold or greater. The finding of antibody in a person suspected of having a recent exposure does not rule out active disease, but should be followed by a second determination two to four weeks later. The absence of a change in these two sera would suggest previous immunity. Reliance on a history of rubella as a means of determining present individual immunity was shown to be valueless in this study. (Tables 2 and 3)

The attack rate here of 50% among susceptible students was

much lower than the nearly 100% attack rate reported in military recruitment camps.[9] This would indicate that the attack rate is proportional to the degree and length of exposure. The intensity of the exposure should be considered when assessing the risk of contracting disease in individual cases.

One interesting case in this group with an illness diagnosed as clinical rubella was shown to have an Echo virus 9 infection. If she had been in early pregnancy, an unnecessary termination of pregnancy may have been performed, or an uncomfortable six to eight months of waiting and worrying may have needlessly ensued. This points out even more the need for early and accurate disgnosis.

History of previous exposure is shown to be a completely unreliable means of determining previous rubella infections. Table 3 clearly shows 85.7% of persons claiming no history of rubella infection had neutralizing antibody present to rubella virus. In adults the clinical course may only slightly approximate that of infections in children.[11a] The characteristic onset is with enlargement of lymph nodes, specifically the posterior cervical chain, post-auricular, and sub-occipital nodes. In children, this manifestation may go unnoticed in the earliest stages, but adults frequently are aware of tender, swollen nodes, and vague malaise for as long as a week before the onset of rash and fever.

By examining children exposed in a closed, institutional outbreak, and by observing those in whom infection has been

induced artifically, [12] it has been shown that the period of viremia and the appearance of virus in the throat commonly appears during the incubation period. This occurs most frequently at about seven days after exposure or at the same time that the lymph nodes begin to enlarge. Virus has been recovered from the throat and from the blood as long as seven to eight days before onset of symptoms. In several cases virus excretion has been demonstrated in the throat 13 days before the rash appeared. [13] Rubella virus has also been demonstrated in rectal swabs collected during the pre-eruptive period, and it has been recovered from the urine around the time of onset of the rash. (See Chart I)

When the rash appears, the infection is already of considerable duration and neutralizing antibodies can first be detected at about this time. It would seem that the rash as in measles is not due to dissemination of virus in the skin, but is an expression of a reaction of antigen - antibody, or hypersensitivity type. Since antibodies are circulating, it is not surprising that virenia can no longer be detected once the rash is fully developed. Persistence of virus in the throat is common for at least a week and may stretch to even three weeks. From Chart I it may be seen that there are varying periods of viral excretion, with urinary excretion being the shortest and least reliable. This pattern is somewhat different from that seen in congenital rubella.[14]

In congenital rubella 32% of throat swabs, 19% of urine specimens, and 12% of rectal swabs were positive in the first month of life. Only 15%, 6%, and 3% respectively were positive in the third month of life. Also in this group, cerebrospinal fluid cultures were found to be positive in a large percentage - 33% - with persistent recovery for over 100 days. Blood cultures for the virus were positive in only two of 600 infants with congenital rubella or documented maternal infection. Infants with the rubella syndrome have been shown to produce specific neutralizing antibody to rubella virus, frequently higher in titer than that present in the maternal serum. This antibody may persist for years following a first trimester fetal infection,[3] and an anamnestic response associated with a new exposure to virus is not involved. The infant responds specifically to rubella antigen, as indicated by the presence of 19S antibody, in the early post-natal months of life or perhaps even in utero. This antibody response occurred in the presence of active replication of rubella virus in the chronically infected tissues of the infant or fetus. Thus, neither immunologic incompetency nor tolerance, if evaluated solely in terms of antibody production, explains completely the persistent viral replication during the post-natal period after congenital rubella infection. The lack of evidence for immunologic tolerance is of particular interest since virus may be produced early in embryogenesis

and then persist in multiple anlagen of the fetus throughout the period of organ differentiation. [31]

In the first trimester the rubella neutralizing antibody present in fetal sera in amniotic fluid, from both rubella infected and control embryos derived from women with a past history of rubella is apparently a 7S γ-globulin. Its qualitative resemblance to the dominant 7S -antibody in simultaneously obtained maternal sera, as well as its quantitative and qualitative resemblance to co-existing poliovirus 2 neutralizing antibody all suggest that this material is of maternal rather than fetal origin.

At birth, large amounts of 7S rubella antibody are also present in cord and early infant sera from both infected and control infants. Subsequently, the levels of this 7S antibody decrease, indicating that this material is also primarily of maternal origin. Apparently, 7S antibody may accumulate in fetal sera between the first trimester and birth.[15]

The data on levels of 19S antibody suggest that primary antibody production may be initiated in utero sometime after the 16th week of gestation. After birth there is a continued rise in the production of 19S antibody. Thus, viral persistence in the early months after birth occurs in the presence of decreasing amounts of 7S - antibody, possibly of maternal origin, and in the presence of increasing amounts of 19S antibody. It remains to be shown whether viral persistence occurs in the presence of

primary 7S -antibody production.

The presence of significant levels of 19S-antibody in the first six months of life as determined by gel filtration, assist in the establishment of the retrospective diagnosis of the rubella syndrome in the event viral excretion cannot be demonstrated. These levels reach their maximum height between the fourth and seventh month after birth.

Since infants with a congenital rubella syndrome are now known to shed virus and are capable of transmitting clinical rubella,[16 & 17] pregnant women should be cautioned to avoid contact with these babies.

The period of viral excretion in adults indicates that the infectious stage is prolonged. While rubella is stated by some to be not nearly as contagious as measles, this would not seem to be true. Attack rates can be shown to vary between 50 and 100% of susceptibles, particularly with long exposure.

Not all infections are clinically apparent. As early as 1953 Krugman and co-workers,[18] demonstrated the occurence of symptom-free viremia in volunteers infected by intramuscular injection of virus. The ratio of inapparent to apparent infections seems to vary with age and other factors, but is at least 1:1.[19] In certain circumstances this ratio may be as high as 6:1.[20]

These findings with respect to the duration of virus excretion, and probable period of contagion in both apparent and

inapparent infections are of practical importance in handling the problem presented by first trimester exposure. Often in such instances exposure has been made with a child or adult who has probably been shedding virus for some days or even a week before rash has developed. Thus, many women may have been exposed without their knowledge.

The prophylactic use of gamma globulin has enjoyed several high periods of use and at present there is much debate concerning its use. As shown by one article,[21] where 15 to 20 ml. of gamma globulin were given within five days after exposure, there was a significant reduction in the incidence of clinical maternal rubella. However, when paired sera were tested from the two groups with a complement fixation method, there was an apparently equal, low frequency of infections as indicated by seroconversion. Five percent of those receiving gamma globulin showed conversion as opposed to three percent conversion in those who did not receive it. Furthermore, exposure 12 to 21 days prior to illness was known by only 45% of the patients with first trimester rubella, indicating that 55% of the patients with clinical rubella could not have received prophylactic treatment.

Table 4 illustrates several striking differences evident after the administration of γ globulin. With gamma globulin, only 1.4% showed clinical rubella within one month. The control group had an 11.1% incidence of clinical rubella

within one month (P= 0.01). Only 1.3% of those given gamma globulin had a proven abnormal pregnancy outcome. The control group showed 3.05% suspected and proven fetal abnormality. The number of proven abnormalities in the control group was only 1.336%. Therefore, it can be seen that at least on the basis of proven abnormality no significant difference exists between gamma globulin administration and control groups.

Table 5 demonstrates that 26% of those mothers with clinical rubella failed to show seroconversion. Serological studies with paired serum specimens must be obtained if this 26% error is to be eliminated.

10% of all women with clinical rubella during the first trimester later have a child with a congenital rubella syndrome recognized within the first month after birth.[21] In Sever's same series of patients with first trimester exposure, but no clinical rubella, only 0.6% had a child with congenital rubella syndrome. There was a significantly greater frequency of white patients who reported first trimester exposure (P 0.1). A history of clinical rubella was given by significantly higher proportion of non-white mothers (P 0.05).

Before a definitive diagnosis of congenital rubella can be made, all of the above factors should be carefully evaluated.

Congenital rubella may be diagnosed as that group of maternal, fetal, and neo-natal abnormalities associated with, but not unique to, maternal infection with rubella virus during pregnancy. At present there are a number of methods available to aid and confirm this diagnosis. One group includes some of those factors already discussed. These are:

> Maternal exposure, including week of gestation of the conceptus is important, as is the length of exposure.
>
> Proof of exposure as determined by paired serum samples for rise in neutralizing antibody titer is definitive.
>
> Maternal virus excretion and recovery from throat, blood, urine or fecal samples is now recognized as a valuable aid. Recovery may be accomplished between the sixth and twenty-fourth day after exposure, depending upon the source utilized.

The final diagnosis of the congenital rubella syndrome must lie in the examination and testing of the infant. No single fetal deformity thought to be associated with maternal rubella infection is pathognomonic of that infection. We are dealing with a syndrome, definable as "a set of symptoms which occur together; the sum of signs of any morbid state; a symptom complex". This diagnosis, therefore, cannot be made on rigid guidelines but must include clinical judgment.

Gregg[3] described congenital cataracts as the first congenital malformation associated with rubella. In the

past twenty five years many new deformities have been accredited to this disease complex which today is recognized as a significant cause of infant deformity.

The first abnormality to be discussed in the outcome of any rubella influenced pregnancy is that of spontaneous abortion. Manson [22], stated in 1960 that "pregnancy wasteage by spontaneous abortion is at least twice higher in women who have rubella than in controls". Other authors, including Sever,[21] show that in their studies there is no major difference between rubella and control groups (P=0.05). (See Table 6) One factor warranting careful consideration concerning reproductive wasteage is the number of therapeutic abortions performed. Unfortunately, many of these abortions are ill-advised, not being performed on any solid clinical basis. I would think that therapeutic abortions influence the statistics in a way which cannot be totally appreciated at first glance, and may tend to lower the number of rubella babies reported.

The most commonly noted defect today is that of cardiacic abnormality. Horstman [11] reported 86% of his study group with a diagnosis of congenital rubella as having significant cardiac defect. Korones [23] reports 100% of his series of 22 with cardiac abnormalities. In every article, heart defect was rated as the most frequent and serious defect found. Patent ductus arteriosus is the most common

defect reported in up to 70% of patients. This is present both as a single defect and also noticed with a wide variety of other cardiac lesions. Peripheral, or valvular, pulmonic stenosis was noted as a single defect in up to 33% of all cases. Ventricular septal defect was also common and may also be found associated with atrial septal defect, patent ductus, or pulmonic stenosis. Hypoplastic left ventricle was reported by Sever [21] both as an isolated and combined defect. Other less common defects include:

1. Persistent left superior vena cava.
2. Hypoplastic left atrium.
3. Hypoplastic mitral valve.
4. Hypoplastic aortic valve.
5. Atrial septal defect
   A. Osteum secundum
   B. Osteum primum and common atrio-ventricular canal

Korones [23] found both tissue and electrocardiographic evidence of myocardial necrosis in seven of twenty two patients. Serial sections of the myocardium revealed severe and extensive necrosis in the absence of inflammatory response. Muscle fibers were swollen, nuclei were pleomorphic and pyknotic, and vacuolar degeneration was extensive in several sections. Both prenatal and postnatal myocardial damage may be caused by rubella. In two patients Krones believed the major pathology to have occurred in utero. These showed a pathologic Q wave inscribed in the initial portion of the downstroke of the QS deflection of

leads I and aVL. Pathologic Q waves in leads II, aVF and the left precordial, absence of an R wave in leads I and aVL, and low amplitude R waves in V6 and V7 were also reported. There were no abnormalities reported in the S-T segments and T waves. After 15 weeks these tracings showed no change to a more normal pattern.

Ina well-documented series of seven patients with EKG evidence of myocardial damage the clinical courses were divided into three groups.

Group I - Active myocardial disease present and progressive in two infants who died within the first six weeks of life. Electrocardiagrams compatible with widespread myocardial injury and destruction. Clinical courses were characterized by the early onset of congestive heart failure, which proved intractable to intensive medical therapy.

Group II - Active myocardial disease subsided in three of five infants who recovered. Their electrocardiagrams initially were similar to Group I, but subsequently mimicked the changes of healing myocardial infarction as seen in adults. Electrocardiagrams after three months continued to show S-T segment and T wave changes indistinguishable from those produced by digitalis therapy. The S-T vector is rotated to a position opposite the mean QRS vector. With a normal QRS, these changes are upward and to the right in the frontal plane, with the S-T segment depressed in the

limb leads. In the horizontal plane the S-T vector is anterior. S-T depression is most marked in the left precordial leads. These changes in the direction of the S-T vector are due to the early onset of repolarization. Repolarization occurs abnormally in the same direction as depolarization, or from endocardium to epicardium. The T vector remains in its usual position but is decreased in magnitude.

Group II also showed EKG findings compatible with left atrial and left ventricular overloading, similar to that seen in acute aseptic myocarditis.[24] Their clinical courses were characterized by the early onset of severe congestive heart failure, which subsided gradually over a two week period. Each of these three infants has detectable cardiomegaly.

Group III - Healed myocardial disease was noted in electrocardiagrams taken soon after birth from two infants who survived. These tracings are described as being similar to adult patterns exhibiting well-healed, extensive anteroseptal and anterolateral myocardial infarction. The electrocardiographic abnormalities did not change during the ensuing three months. Korones suggests that these changes are consistent with myocardial destruction occurring in utero. Slight enlargement without decompensation is also noted.

The second most commonly described finding is that of petechial or purpuric skin rash. This has been detected in 50 to 65% of all patients and is always described to be found in combination with thrombocytopenia. The earliest description of this abnormality was made in 1946,[25] but it has been listed only rarely until after the 1964 outbreak. Thrombocytopenic purpura is recognized as one of the less common sequellae in children and adults. Several authors state that the dramatic rise in frequency of thrombocytopenic purpura with the 1964 outbreak may represent a different biologic strain of rubella. No definite antigenic differences have been detected to date.[11] The clinical picture and laboratory findings in thrombocytopenic purpura vary mainly in degree. (See Table VII) Some patients exhibit a generalized eruption with lesions measuring up to 5 - 6 mm. in diameter. More common are a few scattered petechiae usually found on the head, neck, and shoulders. Both petechiae and purpura are found together in some cases. Purpuric spots are seen in both the superficial and deep layers of the skin. Their color varies from dark blue to bright red.

Total platlet counts vary between 3,300 to 100,000 cu. mm. From 50 to 75% of patients with thrombocytopenic purpura exhibit hepatosplenomegaly. An enlarged liver is slightly more common. Skin lesions frequently disappear

in several days and platlet counts usually return to normal in two to five days. Thus, unless the patient is examined carefully and laboratory studies ordered early, this deformity might be missed.

Several cases exhibit abnormalities of longer duration. One child [26] with extensive ecchymoses and patechiae at birth had persistent hypoplastic anemia and thrombocytopenia. At age two and five months this infant was hospitalized for bone marrow biopsy and transfusion. At birth the platlet count was 58,000 per cu. mm. and ranged thereafter between 1,100 and 25,000 per cu. mm. Extensive crops of patechiae and ecchymoses continued to appear after birth. Bone marrow biopsies showed hypoplasia, reduced megakaryocytes, and a left shift of the myeloid elements. Red cell survival times were markedly diminished with a half-life of twelve days. The peripheral white count remained consistently low, being between 3,700 to 5,000 per cu. mm.

The terminal episode in this child showed congestive heart failure, associated with anemia (hematocrit 6.5%) and multiple intercranial hemorrhages. At autopsy, rubella was isolated from nearly every possible tissue site. Nearly all other studies invariably state that skin lesions are uniformly absent by the eleventh day. Platlet counts usually return to normal in less than two weeks. This child would seem to represent one of the fortunately rare

and unexplainable control simultaneously by rubella virus of many organ systems.

The mechanism for thrombocytopenia has not yet been established. It is suggested by some that inter-action between an anti-platelet factor in the mother's serum and some form of virus-platlet complex in the infant's serum is responsible.[11 & 19] Splenomegaly also suggests that as in some other forms of thrombocytopenic purpura the spleen may be the site of sensitized platlet destruction.

Peripheral blood studies are generally not helpful in establishing the diagnosis of congenital rubella. Leucocytosis ranging from 7,000 to 30,000 per cu. mm. with no consistent pattern of differentiation is the normal finding. Hemolytic anemia, reticulocytosis (6.7% to 11.1%), and increased numbers of neucleated red blood cells (26 to 101 per 100 leucocytes) are also reported for the first 48 hours of life.

Congenital cataract has been found in from one third to one half of all documented cases of congenital rubella associated with the 1964 epidemic. This may occur as a unilateral defect but is more commonly noted in both eyes. Associated but infrequent ocular deformities include microphthalmia in 8 to 13%, and chorioretinitis in 5 to 6%. Unilateral glaucoma has been detected in 9 to 12.5% of those

with cataracts, but its total incidence is unknown since tonometry in most cases was done only in infants with cataracts. There are no reported cases of bilateral glaucoma.

A new defect first described in 1964 is translucent long bone lesions.[27] Radiolucency is seen in the metaphysis of the long bones in both the upper and lower extremity. These were shown in three of five infants examined radiographically by Horstmann.[26] Two of these infants later sustained spontaneous fractures through the radiolucent defect while in the hospital, as did two other rubella infants in whom no X-ray evidence of a bony lesion could be found.

Microcephaly is found in 8% of rubella babies. Other central nervous system defects include a significant incidence of mental retardation. This would frequently be found in microcephalic infants. In congenital rubella, however, normocephalic infants thought to be otherwise normal were also found to be mentally retarded within an incidence approximately 10% higher than could be expected in the population at large. It will be several years before the full incidence of mental retardation can be recognized and tabulated.

Rubella virus may be recovered from the cerebrospinal fluid of rubella infants.[14] Recovery rates may be

very significant (up to 14%)in completely normal appearing infants with a maternal history of first trimester rubella. Of all infants born to mothers affected by first trimester rubella, even if not clinically a congenital rubella syndrome, the isolation rates from cerebrospinal fluid ran high in the first two months of life. (30% and 11%). In the final days of his testing, Phillips[14] notes that ten of fifteen cerebrospinal fluid cultures were positive. The oldest child in his study group included a 194 day old infant with positive cerebrospinal fluid recovery. Horstmann[26] reports five cases with positive cerebrospinal fluid viral recovery. Protein and cells were normal in three and protein alone was elevated in two cases. In other cases, the congenital rubella syndrome reported as negative for cerebrospinal fluid virus recovery there were noted abnormally high protein contents in eight of thirteen children. Four of these eight also showed increased numbers of leucocytes. Protein was also noted to be at the upper limits of normal in three of thirteen children. Sugar content was normal in all instances.

One article that would certainly point the way toward future rubella research is that written by Robinson and Puck.[28] In this article they discuss the possibility of rubella virus producing chromosomal aberrations in man. Interestingly enough, the mother of an infant with trisomy 18 had definite

serological proof of infection with rubella during pregnancy in one study.[21]

Table 1.--Outcomes of Rubella-Complicated Pregnancies by Trimester of Infection[5]

	First Trimester			Second Trimester			Third Trimester		
	No. of pg.	Prenatal death	Fetal deformity	No. of pg.	Prenatal death	Fetal deformity	No. of pg.	Prenatal death	Fetal deformity
Accumulated cases to 1956.	63	4	10	28	2	4	9	0	0
Pitt 1957	16	0	3	4	0	0			
Hill, et. al. 1958	18	0	5	15	1	2	5	0	0
Oxorn 1959	36	6	5	8	0	0	1	0	0
Michaels et. al. 1960	13	4	3	10	0	0	3	0	0
Mullens et. al. 1960	16	4	7	4	0	0	2	0	0
Manson et. al. 1960	202	19	30	276	8	9	96	4	2
Lock et. al. 1961	47	8	12	32	1	1	14	0	1
Pitt et. al. 1961	78	7	13	45	0	1	1	0	0
Accumulated cases 1961	489	62 (12.7%)	88 (18%)	422	12 (2.8%)	17 (4%)	131	4 (3.1%)	3 (2.3%)
Total death and deformity		150 (30.7%)			29 (6.8%)			7 (5.3%)	

Table 2.-- Cincinnati General Hospital Newborn Longitudinal Rubella Study*[7]

Clinical Findings [x]	Number	Virus Positive	Virus Negative
History neg. Abnormalities neg.	276	33	243
History pos. Abnormalities pos.	5	2	3
History pos. Abnormalities neg.	8	1	7
History neg. Abnormalities pos.	11	7	4
TOTAL	300	43	257

* Preliminary results of virus isolation in 300 study infants.

[x] History neg. or pos. for clinical rubella or intimate exposure during first trimester.

Abnormalities present (pos.) or not found (neg.)

Table 3.-- Correlation of History for Rubella and Presence of Neutralizing Antibody*[7]

		Antibody			
		Present		Absent	
History	No.	No.	%	No.	%
"Yes"	54	45	83.3	9	16.7
"No"	28	24	85.7	4	14.3

* Clinic personnel and student nurse groups

Table 4.--Prophylactic Use of γ-Globulin for First Trimester Exposure[21]

γ-Globulin Given (15-20 ml)	145	No γ-Globulin Given	524
Clinical rubella within 1 mo.	2(1.4%)*	Clinical rubella within 1 mo.	58(11.1%)*
Clinical rubella within 2 mos.	3(2.1%)	Clinical rubella within 2 mos.	9(1.7%)
Serology		**Serology**	
Paired serum specimens	43	Paired serum specimens	58
Number at risk serologically	13(30%)	Number at risk serologically	11(19%)
Number of seroconversions	2(5%)	Number of seroconversions	2(3%)
Abnormal Pregnancy Outcomes		**Abnormal Pregnancy Outcomes**	
Exposure only, first trimester		Exposure only, first trimester	
Congenital rubella syndrome	2	Congenital rubella syndrome	2
a. Seroconversion within 2 mo. after γ-Globulin	(1.31%) TOTAL ABN. PROVEN	Suspected congenital rubella syndrome	2
b. Serologic data incomplete		Suspected acute congenital rubella syndrome of the newborn	6
		Maternal rubella, first trimester	
		Congenital rubella syndrome	5
		Suspected congenital rubella syndrome	1
			(3.05%) TOTAL ABN. SUSPECTED AND PROVEN

*Significant difference, X^2 test ($P < .01$)

Table 5.--Serologic Studies of Patients With Clinical Rubella or First Trimester Exposure to Rubella.[21]

1. Clinical rubella	135 Patients
Paired sera available bracketing reported clinical disease	43
Seroconversions	32(74%)
11. First trimester exposure to rubella (No clinical rubella)	615 Patients
Paired sera available bracketing reported exposure	245
Seroconversions	16(6%)

Table 6.--Abnormalities of Children Recognized in Subgroup Through Neonatal Period[21]

Maternal Rubella, 135 Infants		Exposure to Rubella in First Trimester, 568 Infants[x] (No Clinical Rubella)	
Congenital Rubella Syndrome	6	Congenital Rubella Syndrome	4
Suspected Congenital Rubella Syndrome	2	Suspected Congenital Rubella Syndrome	2
Acute Congenital Rubella of Newborn	1	Acute Congenital Rubella of Newborn	6
Reproductive Wastage			
Abortions	11 (10 Therapeutic)	Abortions	15(2.7%)* (Total study: 2.2%)
Stillbirths	3(2.4%)* (Total study: 1.6%)	Stillbirths	16(2.8%)* (Total study: 1.6%)
Neonatal Deaths	1(0.9%)* (Total study: 1.8%)	Neonatal Deaths	14(2.5%)* (Total study: 1.8%)

[x]615 pregnancies resulted in 618 infants; data available for 568 infants.

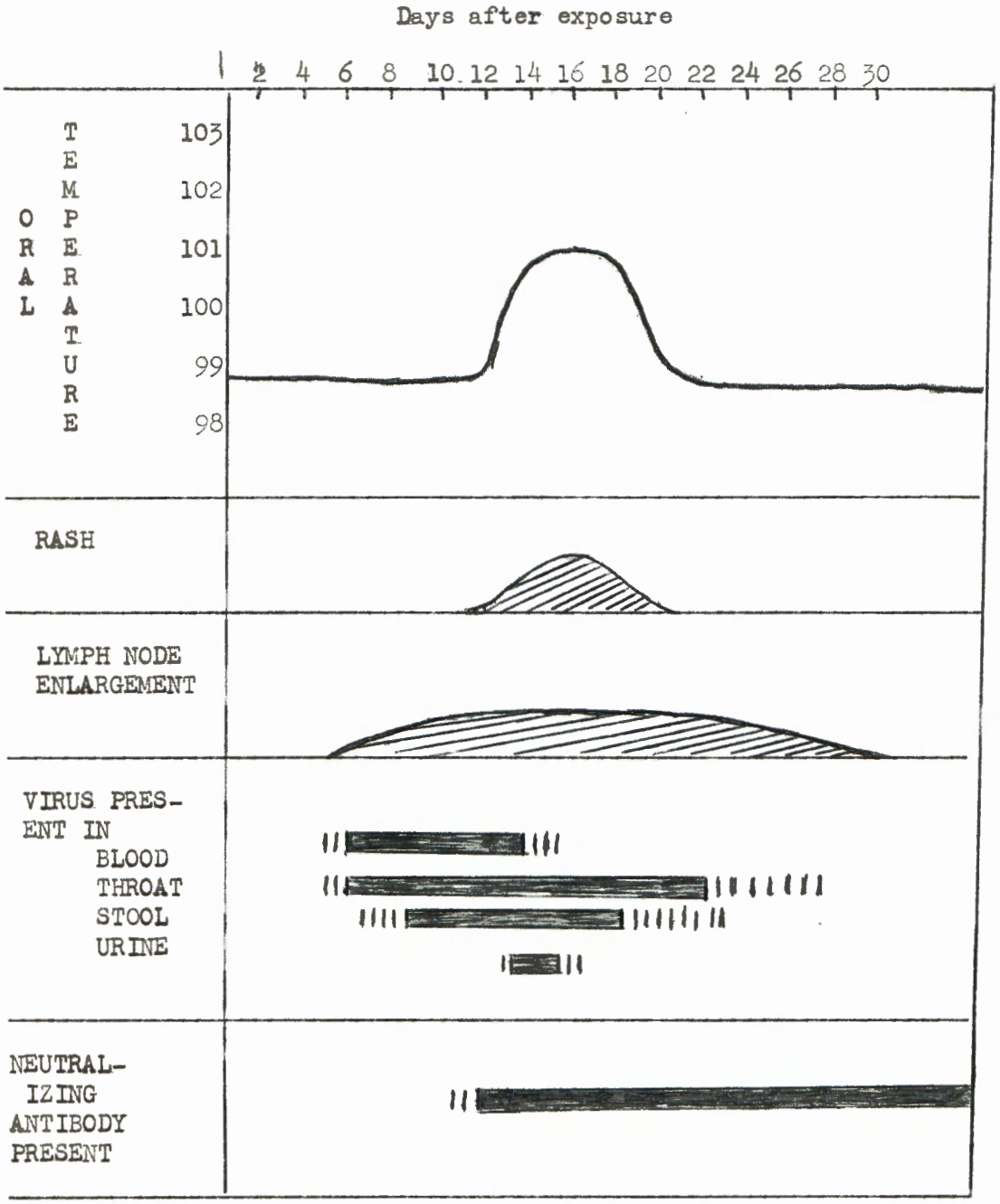
*No significant difference when compared with 41,804 pregnancies in the Collaborative Study Population, x test (P=0.05), based on tables of binomial distribution.

Table 7.--Rubella Syndrome with Thrombocytopenic Purpura[11]

Platlet Counts (per cu. mm.)	Number of Infants	Hepato-splenomegaly	Other Anomalies*	Virus Isolations (Throat) Number Positive	Virus Isolations (Throat) Number Tested
<30,000	3	3	3	3	3
30-49,000	3	2	1	2	3
50-100,000	5	3	4	5	5
>100,000	2	2	1	2	2
Totals	13	10(77%)	9(69%)	12	13(92%)

*Cardiac lesions (9); cataract (5); other (4)

Chart 1.--Schematic Diagram showing time relationships between virus excretion, antibody responses, and clinical manifestations of rubella.



IIIII INDICATES OCCASIONAL ISOLATION

SUMMARY:

Rubella was not recognized as a separate disease entity until as late as 1899. Little was written about rubella during the early twentieth century. Gregg in 1941 described congenital cataract, and stated that it was due to maternal infection by rubella virus during pregnancy.

The largest rubella epidemic in U.S. history occurred in 1964. Between 10-30.7% of first trimester rubella infections will result in fetal death or malformations. The second and third trimesters of pregnancy are also influenced by maternal rubella. A single rubella infection confers lifetime immunity. Eighty five per cent of the adult population is protected by neutralizing antibody. Past history of infection and clinical appearance are of no value in definitive diagnosis. Paired serum specimens for rise in neutralizing antibody titer is the best method of diagnosis, particularly since the ratio of inapparent:apparent infections may be as high as 6:1.

Viremia and viral excretion may be present for two weeks before the rash appears. Adults and children shed virus at different rates and from different sites. Infants with congenital rubella shed virus from several sites for up to sixty days. Unsuspecting adults can thus be infected. Gamma globulin administration significantly reduces signs and symptoms of maternal infection, but in no way can be shown to

reduce fetal risk.

Spontaneous abortion is probably no more frequent in rubella influenced pregnancy. Therapeutic abortion is an all too frequent complication in suspected but unproven maternal exposure to rubella.

Cardiac defect is the most frequent and serious deformity seen in the Congenital Rubella Syndrome. Patent ductus is seen in aprox. 70% of all defects. Most heart defects are multiple. Myocardial necrosis without inflamation is a newly described lesion.

Thrombocytopenic purpura with hepatosplenomegaly is the second most commonly seen.(50-65%) Skin lesions usually appear in a single crop and disappear within five days. Platelet counts also return to normal limits usually within five days. The basic mechanism underlying thrombocytopenia is unknown.

Congenital cataracts, usually bilateral, are seen in 33-50% of the cases. Unilateral glaucoma is present in 9-12% of children with cataract. Other eye findings are frequent.

Microcephaly, often in conjunction with mental retardation, may be seen in 8%. Mental retardation without microcephaly may also be more frequent than thought, and will be seen in older age groups as is deafness.

Rubella induced congenital defects are being recognized every year for the first time, and the possibility of chromosomal aberrations due to rubella is now being evaluated.

CONCLUSION:

Congenital rubella has existed as a separate disease entity for only twenty five years. Its study was given great impetus by the 1964 epidemic in the United States.

The diagnosis of maternal rubella infection is not easily made. Neither past history of rubella infection, nor clinical signs or symptoms are reliable methods of diagnosis. Inapparent rubella infections are possibly more common in adults than clinical rubella. Paired serum samples for rise in neutralizing antibody titer, and viral recovery and culture are the only definitive methods of diagnosis.

The syndrome associated with congenital rubella infrequently produces an isolated defect. The most frequently noticed manifestations include; Cardiac defect, Thrombocytopenic purpura, and Cataract. Many manifestations of this syndrome may not be recognized or appreciated until several years after birth. New malformations are being discovered every year.

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