THE OCULAR MANIFESTATIONS OF CONGENITAL RUBELLA

BY *Stewart MacKay Wolff*, MD

INTRODUCTION

THIS REPORT IS BASED ON AN INVESTIGATION OF 328 CASES OF CONGENITAL rubella in infants and young children seen in our hospital from 1964 to the present. Particular attention is given to ocular involvement, which was present in 175 children.

To our knowledge this is the only prospective clinical investigation of the ocular manifestations of congenital rubella arising from the American rubella epidemic of 1963–4. Most of the children have been followed from the time of their mother's registration in the prenatal clinic to the child's sixth or seventh birthday. In every child the diagnosis of rubella has been proven serologically or virologically. This investigation casts new light on several aspects of the expanded congenital rubella syndrome.

HISTORY

The importance to the developing fetus of prenatal infection with rubella virus was recognized first by Sir Norman McAllister Gregg in 1941.[27] Following a severe rubella epidemic in Australia he examined a number of infants with cataract, congenital heart disease, and deafness. In a paper notable for its originality and brilliance of clinical acumen he described for the first time the relationship between this triad of congenital deformities and gestational rubella. Looking back over Gregg's original paper the reader is impressed with the astuteness of his observations and the relative completeness of his clinical descriptions. Within a short time ophthalmologists around the world were able to cite similar cases, confirming the accuracy of Gregg's initial observations.

The initial studies of Gregg in 1941, of necessity statistically fragmentary, covered 78 cases in which there was ocular involvement with

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congenital rubella.[27,28] Swan, inviting the joint efforts of numerous Australian researchers, was able between 1942 and 1946 to find 42 more Australian cases for a total of 120 cases.[84] Further reports by Reese, Rones, Erickson, Groenthal, DeRoetth and Green, Long and Danielson, Guerry, Gore and Potts, and Clayton Jones all added from 2 to 40 cases each to the world literature, confirming the accuracy of Gregg's initial observations. Franceschetti and Bourquin[24] summed up the world literature in 1946 and were able to find 479 cases of probable ocular rubella, of whom 274 had congenital cataracts. In the next ten years there were many additional clinical reports of children affected by prenatal rubella. Studies by Tondury and Smith,[87] Lundstrom,[43] Sever,[79] and Alfano,[2] among others, added hundreds of cases of rubella embryopathy to the world literature. Studies were principally retrospective, however, emphasizing the salient features of clinical congenital rubella in limited populations, or focusing on specific clinical problems within the congenital rubella syndrome. The only prospective studies have been those emanating from the Australian epidemic of 1941. Menser et al.[46] and Hertzberg[35] recently reported the findings of 50 individuals most severely affected by that epidemic. Their reports serve as invaluable sequels to the original observations of Gregg.

THE RUBELLA VIRUS

While Gregg's observations and those of others from 1941 to 1962 established beyond doubt the viral etiology of the rubella syndrome, efforts to study the disease further were frustrated by inability to isolate the virus in the laboratory. Two dramatic events were soon to change the course of scientific history as it related to congenital rubella, kindling new interest in rubella embryopathy. The first was the isolation of the rubella virus in 1962; the second, coming soon thereafter, was the major rubella epidemic that swept the country in 1963–4.

In 1962 Parkman et al.[63] recovered the virus from Army recruits and demonstrated its cytopathic effects. Almost simultaneously Weller and Neva,[94] studying a group of young adults in a school population, were able to recover the virus from nasopharyngeal swabs and described its cytopathic effect on African green monkey kidney cultures.

The virus itself could not be passed through a Millipore filter smaller than 300 μ, could be heated only to +56°C without significant loss of infectivity, could be stored for a year at −50°C, and was destroyed by ether and sodium desoxycholate. It would not affect either hemagglutination or hemadsorption. Further studies by Phillips revealed the virus to be highly variable in morphology, with surface projections

similar to those of myxoviruses, suggesting that it might be a paramyxovirus.[65] In cross-section it measured 50 to 250 μ, survived in a pH range of 6.8 to 8.1, could be stored dry for a month, and was resistant to idoxouridine (IDU), tetracycline, fluorocarbons, thiomersal, and sodium bisulfite. It was destroyed by chloroform and formalin. Under the electron microscope the virus was of variable morphology with irregular surface projections and particles on its external membrane, each particle measuring between 4 and 12 μ in length.[7]

In AGMK tissue culture the virus was observed to block the cytopathic effect of other viruses and was seen to produce cytopathic changes in primary human amnion cell cultures.[96] The involved cells showed nuclear changes characterized by aggregates of basophilic material in small and, later, in larger clumps. Concurrently prominent eosinophilic bodies were seen in the cytoplasm in intimate association with the basophilic masses.

Maternal infection with rubella virus is often a clinically insignificant disease characterized by fever, lymphadenopathy, arthralgia, and sometimes a morbilliform rash. More often than not there are no signs of illness. During the brief period of viremia in the pregnant woman, generally within ten to twelve days of maternal infection, the virus crosses the placental barrier and infects the fetus.[44] Hematogenous spread of the virus in the fetus results in the establishment of clones of virus-infected cells which may shed virus for months or years after the initial infection. Studies by Rawls, Desmyter and Melnick indicate great variability in the number of cells infected at any one time.[68] In their study of rubella-infected abortuses the number of cells infected ranged from 1 in 1,000 to 1 in 250,000 cells. It can be concluded that the embryo contains foci of infected cells shedding virus which may in time affect many other cells in the process of development. Because all tissues are not infected at the same time and the distribution of the infected cells is uneven, there is wide variation in the clinical picture of congenital rubella.[5] Moreover this and other studies indicate that the persistence of virus may be as important as the concentration of virus.[27,66] Instances of preconception maternal rubella have been recorded and several will be reported in this investigation. Further evidence of viral persistence is suggested by the irregular and uneven involvement of different parts of the same organ system in any one fetus, and by the presence of virus in the excreta for long periods after birth. Virus has been cultured from the infected lens as long as 35 months after birth,[48] and in a recent study one of Gregg's original patients (#47) was discovered to be excreting rubella virus in the urine

29 years after her original and only rubella infection.[47] Specifically there are few parts of the body from which rubella virus has not been recovered; of interest to the ophthalmologist is the fact that, along with the lymphoreticular system, there is no part of the body from which virus may be recovered more regularly than from the cataractous lens.[4]

THE INCIDENCE OF RUBELLA VIRUS EMBRYOPATHY

After Gregg published his original observations on the Australian epidemic of 1941, many investigators felt that the likelihood of fetal involvement where there was maternal rubella in the first trimester was in the neighborhood of 100 per cent.[24] In a study carried on before the isolation of the virus permitted the development of modern serological techniques, Lundstrom reported that the incidence of life-altering disability in the offspring of mothers with a history of clinical rubella in pregnancy was 10 to 15 per cent: 2 per cent with bilateral cataracts, 6 per cent with severe deafness, 1 per cent with disabling congenital heart disease, and 1 to 1.5 per cent with severe mental deficiency.[43] More recent studies, based on laboratory confirmation of the disease, suggest that the risk to the fetus is much higher. It is believed that if there is clinical maternal rubella in the first month of pregnancy the chances of significant embryopathy rise to more than 50 per cent.[34] Prospective studies in a population of 6,000 pregnant women studied serologically and virologically underscore the high risk to the fetus if there is clinical maternal rubella in the first trimester.[79] The classical signs of clinical rubella, rash, arthralgia, lymphadenopathy and fever, are often absent. Consequently the risk of rubella embryopathy where there has been exposure to, but not history of, clinical rubella at any time in pregnancy cannot be assessed without reliance on diagnostic laboratory methods.

THE RUBELLA EPIDEMIC OF 1963–4

The second event to alter dramatically the scientific understanding of congenital rubella was the epidemic of 1963–4. That epidemic, coming fortuitously on the heels of the isolation of the rubella virus, gave investigators an unparalleled opportunity to gain a clearer comprehension of congenital rubella virus infection.

In the American epidemic of 1963–4 it is estimated that there were 12.5 million cases of rubella in a twelve-month period. Of these cases 52,500 were in women in the first trimester of pregnancy. 10,500 of their offspring, of whom 8,400 are still living, had moderate to severe congenital rubella. 3,780 of these children are deaf, while 1,680 are classified as deaf and blind.[54]

The volume of clinical and histopathological material emanating from investigations of that epidemic is well known to the reader. It afforded an opportunity for the clinician to confirm and even expand Gregg's findings and, with the aid of recently developed laboratory methods based on the isolation of the virus, to find laboratory support for the clinical diagnosis. In addition to the triad of cataract, congenital heart disease, and deafness, they were able to add hepatosplenomegaly, thrombocytopenia and purpura, psychomotor retardation, dental deformity, bone lesions, general growth retardation, and inflammatory central nervous system lesions to the syndrome, which was soon labeled the expanded congenital rubella syndrome.

THE HISTOPATHOLOGY OF CONGENITAL RUBELLA

The histopathology of the rubella syndrome as it affects the eye has been described in detail by many authors.[6,83,87,88,95,100,101] Every part of the eye may be involved, but clinical importance is attached to the cytopathic effect of virus on lens, cornea, iris, ciliary body, and retinal pigment epithelium.

Cataract is most likely to follow maternal rubella infection occurring between the second and eleventh weeks of gestation, the period of maximum blood supply to the lens.[44] Primary and secondary fibers are formed in the first eight weeks (12–28 mm stage) and invariably it is these fibers that are involved, the cytopathic effect of the virus delaying their development.[55] The retention of nuclei in the lens fibers is characteristic of rubella cataract and suggests this retarded development[99] (Figure 1). The lens capsule, which forms at the eleventh week, is not visibly affected by rubella virus. Further the lens develops large areas of necrosis.[83,86] Cataract may extend to involve peripheral as well as central cortical fibers, sometimes progressing to total cataract. The areas of necrosis and liquefaction of the cortex tend to be central, however, confirming the clinical observation of a denser central opacity surrounded by a rim of more normal capsule and cortex. Unlike other types of congenital or toxic cataract, there is little posterior migration of the lens epithelium or variation in the morphology of the anterior polar cells. The persistent nuclei in the central mass of the lens, normally free of nuclei, are typically karyorrhectic. Their presence is virtually pathognomonic for rubella.[101] The rubella cataract, customarily swollen and pushing the iris forward to reduce the depth of the anterior chamber,[2] may on occasion be thin and almost membranous, but is rarely without the characteristic nuclei noted above (Figure 2). It is worthy of mention that the rubella virus has been found more consistently, and in greater concentration, in the lens than in any other

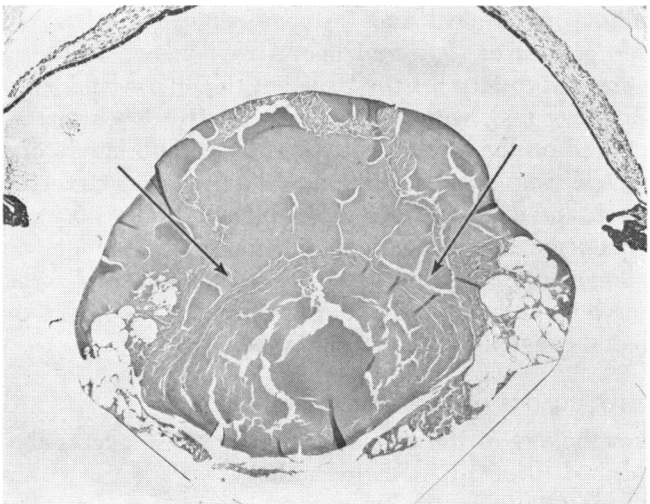


FIGURE 1

Congenital rubella: An intumescent cataractous lens showing cortical fragmentation and liquefaction. The nucleus is preserved (*arrows*).

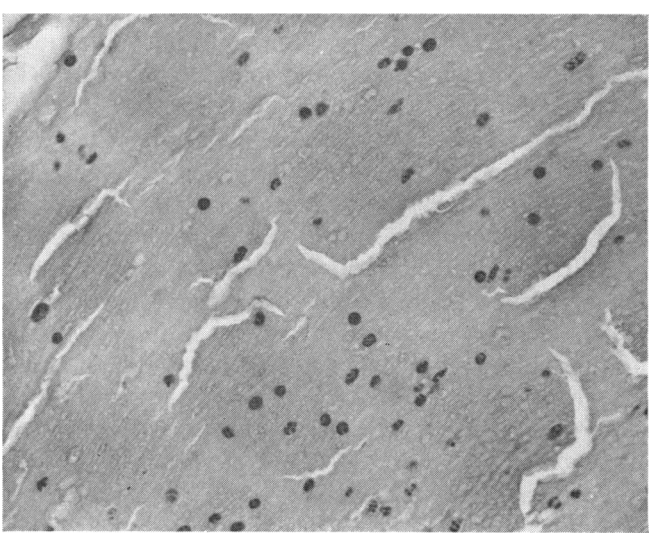


FIGURE 2

Congenital rubella: Karyorrhectic nuclei in lens nucleus.

ocular tissue.[4] Up until one year of age the virus may be recovered from virtually every rubella cataract,[26,37,74] and has been recovered from the lens of one child two years and eleven months of age.[48] The virus has also been recovered from perfectly clear lenses in rubella babies.

The histopathology of the corneal changes in rubella is not so clearly defined. In patients with congenital glaucoma, megalocornea, and buphthalmos it is not surprising to observe corneal edema with endothelial striae. In at least one instance an apparent break in Descemet's membrane was implicated in hydrops of the cornea.[101] Zimmerman has suggested the possibility of corneal edema as a result of prenatal glaucoma.[101] Often, however, the corneal edema present at birth in patients with congenital rubella is transient and not obviously associated with glaucoma. Inapparent viral involvement of the developing corneal endothelium may be implicated, delaying elaboration of Descemet's membrane and adversely affecting corneal transparency. Without a doubt there is active virus in lens, iris, aqueous, and tears, often accompanied, in later fetal life and infancy, by a non-granulomatous cellular response in the anterior chamber. It is also known that virus can be demonstrated frequently in tissues that appear quite normal. It is not known which of these factors, acting singly or in concert, or perhaps some other factor as yet unknown, is most important in the production of the observed corneal changes (Figure 3).

The iris and ciliary body develop about the seventh or eighth week of gestation. Infections existing at that time predictably may produce delay and disorder in the normal development of those two tissues. Characteristic pathological findings at autopsy are atrophy of the iris stroma, hypoplasia, or even absence of the dilator muscle of the iris, and vacuolization and focal necrosis of the pigment epithelium of the iris and ciliary body (Figure 4).[6] Failure of cleavage of the angle of the anterior chamber is also a frequent finding in congenital rubella eyes.[76,87] These changes, characterized by interruption of normal patterns of development without evidence of inflammation, almost certainly occur before the development of an immune response in the fetus. Zimmerman and Font[100] were the first to describe the virtually diagnostic non-granulomatous uveitis with diffuse and focal infiltration of the anterior uvea by lymphocytes, plasma cells, and histiocytes which characterize the infant eye in congenital rubella. Such changes must occur in later fetal life or in the early neonatal period. The existence of a chronic iritis in these eyes has been confirmed by the observations of Wolter and others.[95,97] As will be seen later, the author has not observed

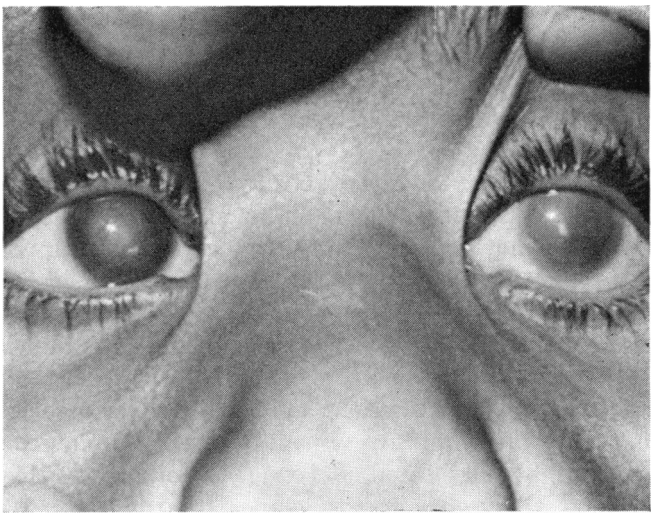


FIGURE 3
Congenital rubella: Corneal haze.

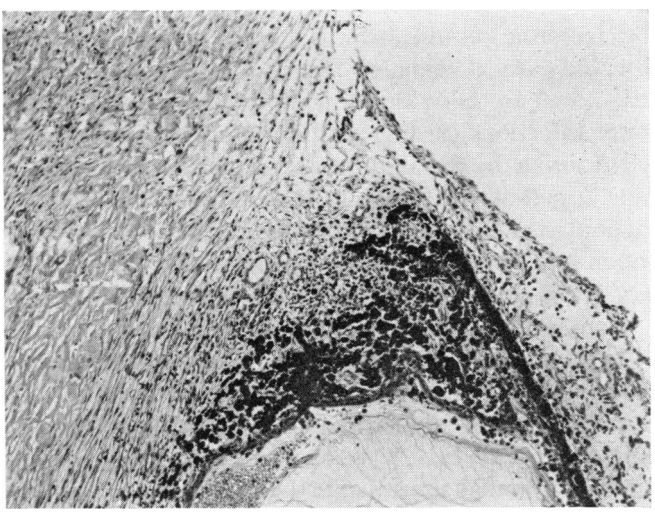


FIGURE 4
Congenital rubella: Ciliary body and iris, non-granulomatous inflammatory infiltration, focal necrosis with pigment aggregates and dispersion. Hematoxylin-eosin, × 80.

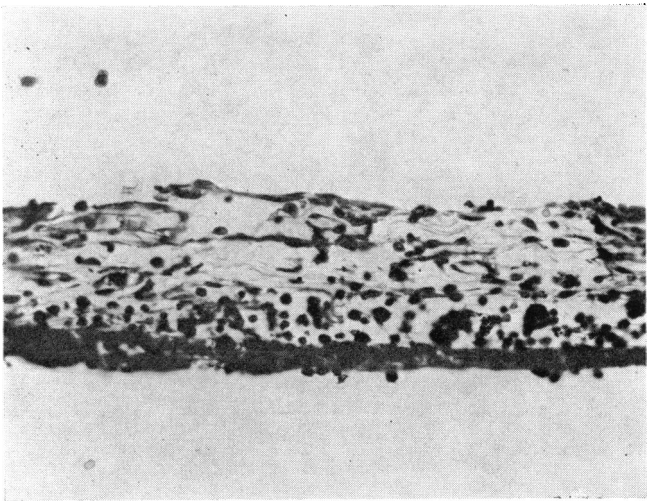


FIGURE 5

Congenital rubella: Iris showing hypoplasia of the dilator muscle, non-granulomatous inflammation with aggregation and dispersion of pigment. Hematoxylin-eosin, × 250.

a clinically active iritis in any of the children in this series. Evidence that it may exist, however, is beyond dispute[41] (Figure 5). Iris atrophy or hypoplasia, a regularly observed phenomenon in children with the rubella syndrome, is almost certainly the effect of viral cytotoxicity. Similar conclusions may be drawn concerning the focal necrosis of the ciliary epithelium, which, along with the focal necrosis of the pars plicata and the pars plana, is considered by the pathologist to be characteristic of rubella.[101] Together the changes in the iris and ciliary body, focal atrophy and cellular infiltration, suggest the two periods of prenatal response to the virus. The first period is characterized by unhindered viral growth in the absence of fetal immunity. During this period there is slowing of replication and even death of developing cells with resultant organodysgenesis. The second period occurs later in gestation and afterwards, and is characterized by an inflammatory response which may represent in whole or part an attempt by the fetus at an immune response to the presence of virus.

Similarly changes in the anterior chamber angle indicate the cytopathic effect of virus in delayed or altered development there. To the characteristic changes in the failure of normal angle cleavage must be added abnormalities of the insertion of the ciliary muscle and changes

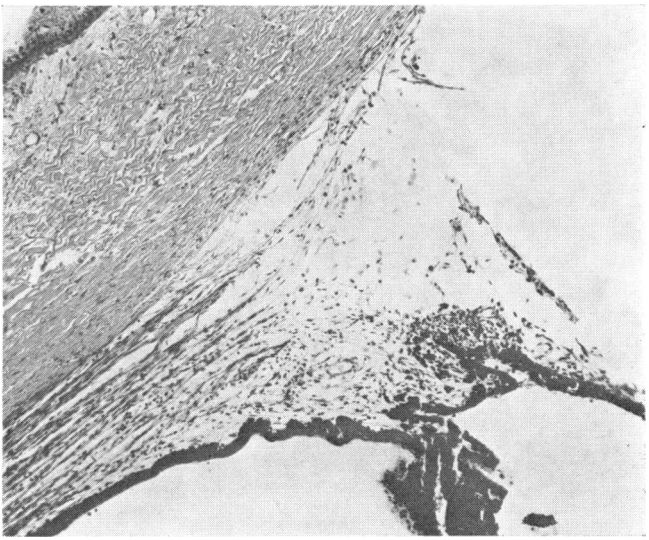


FIGURE 6

Congenital rubella: Incomplete development of the angle, forward insertion of the longitudinal fibers, and hypoplasia of scleral roll and trabecular meshwork. Anterior insertion of base of the iris. Hematoxylin-eosin × 85.

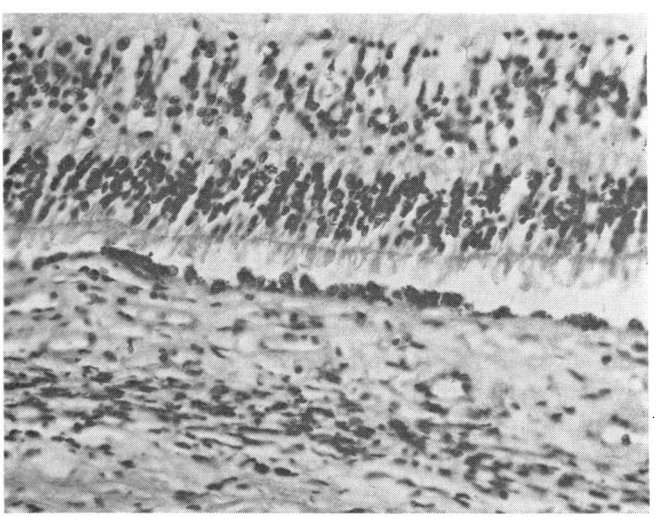


FIGURE 7

Congenital rubella: The retinal pigment epithelium. Uneven distribution of pigment granules. Hematoxylin-eosin, × 235.

in the chamber angle secondary to chronic inflammation and intumescence of the lens[76,87,92,101] (Figure 6).

Original observation of the retinopathy of rubella is attributed to Mitchell,[27] who, according to Gregg, reported a case in which there was a unilateral cataract and the fundus of the other eye "appeared pale with some scattered irregular spots of pigment ..." It frequency was later appreciated by Gregg and the Australian investigators.[28,29,36] Histopathologically the changes are attributable to an uneven distribution of pigment in the cells of the retinal pigment epithelium, especially in the posterior pole (Figure 7). In later fetal life and in infancy the underlying choroid may be infiltrated with inflammatory cells, suggesting an inflammatory response to the presence of virus there.

CLINICAL INVESTIGATION OF CONGENITAL OCULAR RUBELLA

"Serendipitous" was the word used by Alexander to describe the fortuitous occurrence of a major rubella epidemic only months following the isolation of rubella virus in the laboratory.[101] It would not be inappropriate to use the same word to describe the relationship of the rubella epidemic of 1963–4 to the origins of this clinical study. In 1959, with the support of the National Institutes of Neurological Diseases and Blindness, a collaborative program was organized to study the causes of perinatal death and postnatal neurosensory disorders. This study had enrolled approximately 5,000 children from the community at large in a program of periodic medical examination from the time of their mother's registration in the prenatal clinic to the child's eighth birthday. Every mother registered in the program was subjected to a complete battery of serological tests; residual unused sera were frozen and stored. During the period of the rubella epidemic in 1963 and 1964 1,200 newborn children were registered in this study, 139 of whom acquired some of the stigmata of congenital rubella. When it became apparent that the rubella epidemic was of major proportions, it was not difficult to expand the study to include other children in the area affected by congenital rubella.

The remaining 189 children were attracted or referred to this clinic, which soon became the center for the study of rubella in this community. The latter group, then, is a more selected population, representing perhaps half of the children affected in this community, probably those most severely affected.

Since 1965 American studies of rubella as it affects the embryo have covered in detail the pathogenesis of the rubella syndrome,[99–101,97,87,6,

[7,95] and its epidemiology.[77,79,34] Clinical studies have been principally retrospective and have underlined its effects on those most severely affected.[9,83,87,88] Many of the retrospective studies are, however, statistically biased, and there is no prospective study to our knowledge which has been followed to its conclusion, particularly with application to the vast American experience acquired in the severe rubella epidemic of 1963–4.

Of the 328 children reported here, 243 have been followed for seven years; 70 have been lost to follow-up; 15 are known to have died. One hundred and seventy-five of the 328 (53 per cent) are known to have at least one of the ocular stigmata of congenital rubella. Fifty-nine instances of ocular rubella (42 per cent) were found in the 139 children with proven rubella, born of 1,200 pregnancies enrolled under the original NINDB collaborative investigation (Chart 1).

The 15 patients known to have died were among those most severely affected. Autopsies, where permitted, were notable for the multiplicity of viral-induced teratogenic disorders. The principal defect in 5 was bilateral cataract, and in 2, glaucoma. One had retinopathy alone. The rubella virus was grown from the aqueous of one who was thought to have normal eyes. One was not examined while alive. The remaining 5 had no detectable eye disease and were recorded at autopsy as having normal eyes.

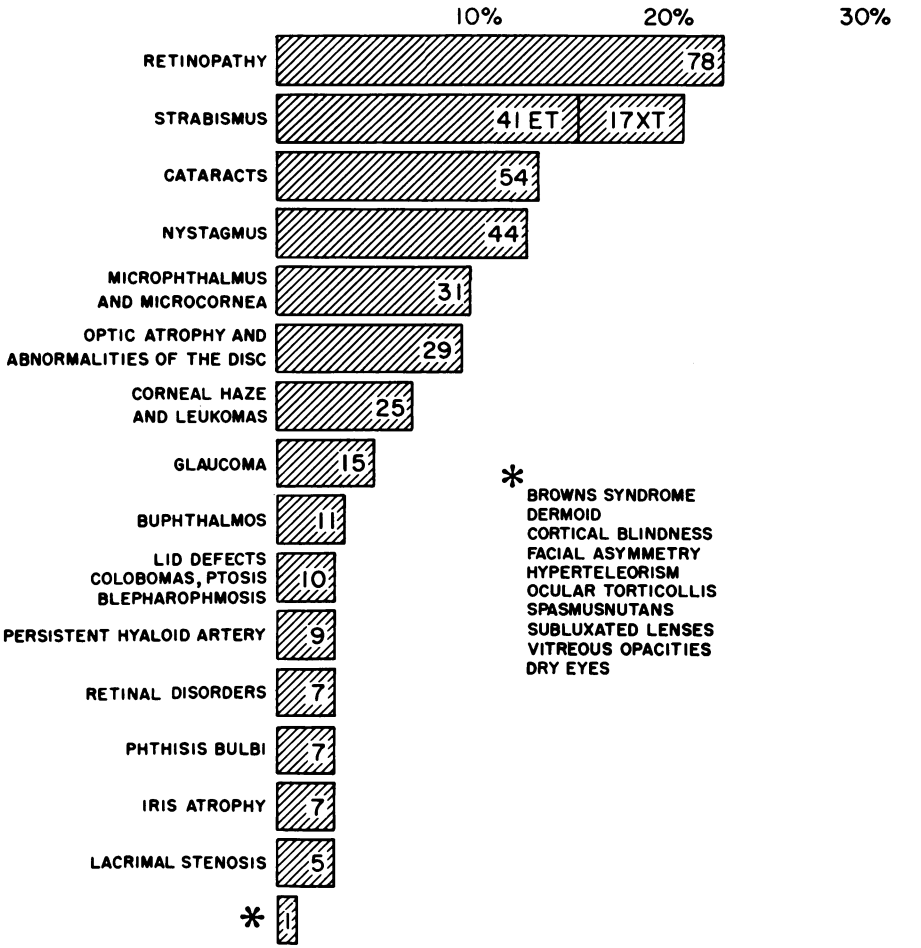
CONGENITAL RUBELLA CATARACT

Of the 54 patients with cataracts in this series, 44 had bilateral cataracts, 10 had unilateral, for a total of 98 rubella cataracts. Sixty-eight cataracts were operated upon. In 6 instances only one of bilateral cataracts was operated upon. Four unilateral cataracts were operated upon. Twenty-nine patients had bilateral cataract surgery. Nine patients with bilateral cataracts were not operated upon. One of these was lost to follow-up, 3 died, 5 were not operated because their vision was adequate for their purposes, generally better than 20/100.

Of the 68 rubella cataracts operated upon, 6 were removed by discission and lavage, 2 by aspiration without iridectomy. The remaining 60 were removed by aspiration of the lens and simultaneous iridectomy, generally a Franceschetti corepraxy. In the postoperative management of these rubella cataracts great emphasis was placed on postoperative mydriasis for at least three months after surgery, and sometimes longer. Topical steroids were also routinely employed for as long as it was necessary to control the frequently severe anterior chamber reaction.

The average vision of aphakic eyes fitted with spectacles was 10/200, with a range of no light perception to 20/50. Such poor acuity does not

CHART 1. INCIDENCE OF ASSOCIATED OCULAR DISORDERS IN 328 CASES OF CONGENITAL RUBELLA



take into account those 22 eyes in which vision could not be assessed because the patients were too young or mentally retarded, or who have died or been lost to follow-up.

Severe inflammation after cataract surgery, sometimes leading to phthisis, is common to all series and was present in 4 of 68 eyes.

Early surgery has been our practice. The age at operation in the series reported here ranged from three weeks to five years, with a median age of six months. Secondary procedures, further aspiration of lens material and discissions of pupillary membranes, were infre-

quent (22 per cent), and were usually performed later without complication. Efforts have been made to fit the children with spectacles as soon after surgery as possible; most wear a single vision reading glass because we have felt that near acuity is more important to a child, who finds his range of interest limited by what he can grasp. Bifocals are prescribed after two years of age.

Because very few of the patients born in 1964 and 1965 were fitted with contact lenses in the early postoperative period, no statistically valid conclusions can be drawn from this series as to the efficacy of early contact lens fitting on eventual visual acuity.

The results of cataract surgery in children with the congenital rubella syndrome have been the subject of much controversy.[14,17,36,64,71–74,97] In the Australian series, following the 1941 epidemic and up to 1949, a total of 204 cataracts was observed by Swan and coworkers, 54 of them unilateral.[86] In none of the early papers based on that series was there any discussion of the results of cataract surgery. The cataracts were removed generally by repeated discission which "frequently proved more difficult than usual" because of the toughness of the dense central portion of the lens.[27] Gregg commented only that in one case of hydrophthalmia trephining was followed by "shrinkage of the eye."[28] Hertzberg, in a later review of the 27 patients with rubella oculopathy from that series, reported 10 of the patients aphakic, 7 bilateral, and 3 unilateral, with 2 of the patients having disorganized or shrunken globes and 9 of the 10 patients having vision of 20/80 or less.[35] Murphy et al., reporting on a somewhat later series of 14 congenital cataracts, reported that 1 patient lost both eyes after cataract surgery, 1 patient lost the only eye that was operated upon, 3 patients lost one eye but had satisfactory surgical results in the other, while the remaining 8 patients had satisfactory surgical results on the operated eye or eyes.[53] His surgical technique was not described at that time.

Scheie and associates, reporting the results of surgery on 49 eyes of 33 patients with congenital rubella cataracts, indicated that surgery before the age of 12 months was associated with poor technical and visual results.[73–75,97] In every eye, because of the rigidity of the iris and the characteristic difficulty in dilating the pupil in these children, a sector iridectomy was performed. Cataract surgery was undertaken some weeks later, sometimes with discission alone, but in most cases with discission and aspiration. In those eyes operated upon before twelve months the postoperative complication rate was 55.2 per cent (29 eyes). Ten of these eyes became either phthisical or had to be enucleated. One of this group had an iridectomy alone, the eye developing a severe postoperative iridocyclitis before the cataract could be

removed. After one year of age, however, Scheie's surgical and visual results have been better, with only 33 per cent complications (6 of 20 eyes). Three of these were phthisical or had to be enucleated. After 18 months his complication rate fell to 21 per cent. The over-all complication rate in Scheie's series was 44.9 per cent; 13 of the 49 eyes in the series were phthisical or had been enucleated.

Cordes established a set of criteria for congenital cataract extraction which are still applicable. The ideal operation should be a single procedure; removing almost all the lens cortex and nucleus and, providing the pupil can be dilated, leaving an intact pupil; involving a minimal risk of iris prolapse or adhesions to the corneal wound; leaving posterior lens capsule and vitreous undamaged; and not being complicated by secondary glaucoma or retinal detachment.[14,16] Most ophthalmic surgeons attempt to make congenital cataract surgery a one-stage procedure, aspirating the lens in toto where possible and performing secondary procedures only if necessary. They should expect vision in the neighborhood of 20/200 bilaterally, probably never better than 20/80.[35] There is no proof in the literature or in common surgical experience to suggest that cataract extraction in unilateral cataract will produce a worthwhile visual result. An exception to this generalization occurs where there is a vigorous postoperative program in which the operated eye is fitted with a contact lens and the opposite eye occluded. Under these circumstances some highly motivated children may be able to obtain useful vision in a unilaterally aphakic eye.[64]

While much attention has been drawn to phthisis after cataract surgery, we have observed phthisis in this series in several other connections.[7,8] As noted earlier, Gregg reported phthisis following glaucoma surgery in one of his original patients.[28] In this series 7 eyes became phthisical, only 4 of them following cataract surgery. The 4 eyes developing phthisis after cataract surgery were all microphthalmic. One eye, also aphakic, became phthisical one year after a cyclocryothermy procedure for postoperative glaucoma. One eye became phthisical after a Gundersen flap had been pulled over a neglected corneal ulcer, and one highly myopic eye became phthisical after retinal detachment surgery.

GLAUCOMA

Fifteen of the patients in this series had clinical evidence of glaucoma. In 14 of the children the glaucoma was bilateral. Eleven eyes were buphthalmic. All 15 patients were operated upon, many of them more than once. A total of 82 operations was performed on the 29 glaucomatous eyes. The primary operation, where the angle was visible, was

goniotomy. If necessary, and where possible, that operation was repeated. Where the angle could not be visualized or where more than two procedures had to be performed, cyclodiathermy and, more recently, cyclocryothermy were performed.

Two patients are deceased. One enjoys 20/25 vision in each eye with myopic correction. Two have 20/40 in the better eye, 5/200 or less in the poorer eye. Two enjoy 20/200 vision in the better eye with 5/200 or less in the poorer eye. The 8 remaining children have no visual acuity in either eye, and 6 of them are in the local school for the blind. Eight of the 15 still require medical management of their glaucoma.

All but 3 of the 15 glaucoma patients had a corneal haze which has tended to persist (Figures 8 and 9); 2 were microphthalmic, 2 highly myopic, and 5 had an associated strabismus. Ten of the patients have bilateral buphthalmos, 1 unilateral buphthalmos.

The reported incidence of glaucoma in congenital rubella is variable. Swan reported "a few," Geltzer 4 of 24,[26] Sever 1 of 21,[79] Alfano 10 of 21,[2] Ikui 1 of 128.[39] Sears[76] estimated that 10 per cent of congenital rubella infants had glaucoma. A summary of retrospective studies up to 1969 reveals that of 730 reported cases of congenital rubella, 22 had glaucoma while 230 had cataracts. The literature from which these figures were derived points up not only the relative infrequency of glaucoma but also the difficulties inherent in making the diagnosis.

In our study of a larger population, 175 of whom had one or more of the ocular stigmata of congenital rubella, 54 (30 per cent) had cataracts, 15 (9 per cent) had glaucoma. Originally it was thought that the coexistence of glaucoma and cataracts was rare.[76] Of the 5 patients with both disorders reported here, 4 patients with bilateral glaucoma had bilateral cataracts. One patient had bilateral glaucoma and a unilteral cataract. The data indicate that the incidence of glaucoma in cataract patients (5 of 54, or 9 per cent) is identical to that found in the larger population of ocular rubella (15 of 175 or 9 per cent); and that the incidence of cataract in rubella children with glaucoma (5 of 15, or 33 per cent) is similar to that in the larger population (54 of 175, or 31 per cent). From these data the conclusion is drawn that, in congenital rubella, glaucoma and cataract are not mutually exclusive but occur together at the frequency expected of coincidental events occurring independently (Chi square = 0.053).

CONGENITAL RUBELLA RETINOPATHY

Seventy-eight of the patients were observed to have rubella retinopathy, of whom 65 had bilateral involvement, 13 unilateral involvement.

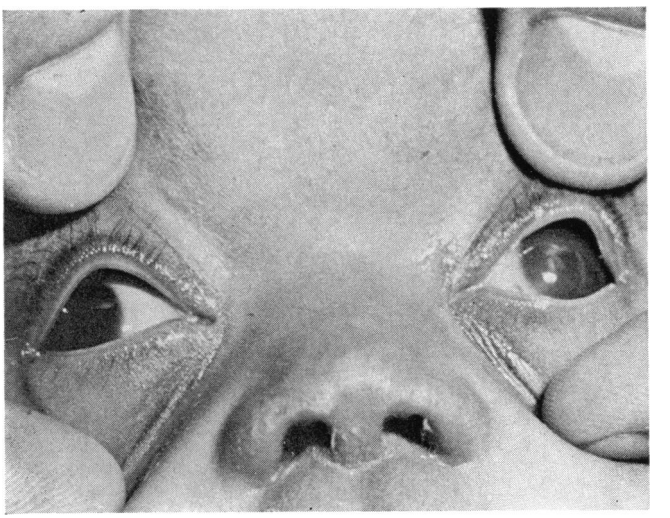


FIGURE 8
Congenital rubella: Persistent corneal haze. Picture taken in newborn nursery in 1965.

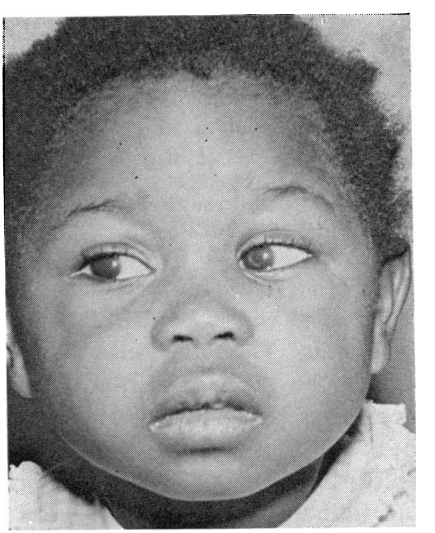


FIGURE 9
Congenital rubella: Persistent corneal haze. Picture taken in 1968.

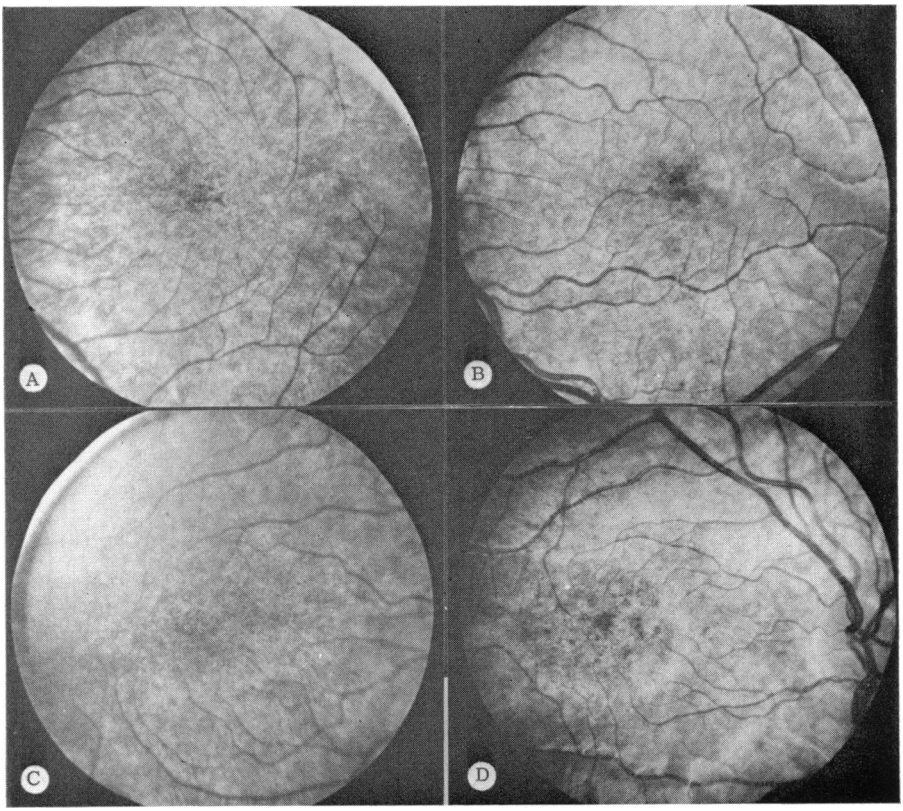


FIGURE 10

Congenital rubella: Four examples of retinopathy. (a) Left eye, visual acuity 20/50; (b) Left eye, visual acuity 20/30; (c) Right eye, visual acuity 20/40; (d) Right eye, visual acuity, 20/40.

In those children whose vision could be tested and who had neither cataract, glaucoma, nor other cause for poor visual acuity, vision ranged from 20/20 to 20/60. Median vision was 20/25. Seven patients had corrected vision of 20/40 or less. The retinopathy of rubella had been considered until recently to be diagnostically valuable, non-progressive, and functionally insignificant. While it is difficult to correlate visual acuity with the appearance of the macula, the 7 patients noted here had severe pigmentary disturbance in the affected eye or eyes. (Figure 10). Moderate degrees of retinopathy were not associated with defects in visual acuity. Electrophysiological studies were not performed in any of these 7 patients. A review of electrophysiological studies by Krill, Franceschetti, and others indicates that electroretinograms may be

abnormal in as many as half the patients with rubella retinopathy while electrooculograms indicate that pigmentary changes do not affect pigment epithelial function.[23,42,98]

Recent evidence has suggested that the retinopathy of rubella may be progressive.[12] The writer's experience has been to confirm the progressive nature of the retinopathy; I have seen 9 patients in whom examination at infancy revealed no retinopathy, while examination at the age of seven indicated marked changes in the retinal pigment epithelium.

As noted previously, the original recognition of retinopathy as a part of the congenital rubella syndrome is attributable to the Australians. Mitchell described a mild retinopathy;[27,81] Gregg later described a severe retinopathy as "like a piece of coarse Scotch tweed used for a sportscoat over which pepper had been thrown."[29] In the literature retinopathy is stated to occur in about 40 per cent of the patients. It may be unilateral or bilateral, central or peripheral, irregularly distributed in the eye, mild or marked. Pleomorphism is the rule. Descriptions have ranged from blotchy and mottled to finely stippled and bone-spicule like.[23,42]

Studies underlining the progressive nature of the rubella syndrome after birth have emphasized continuing opacification of the cataractous lens[28] and progressive atrophy of the iris stroma while overlooking the possibility that the same may be true of the retinopathy. In fact it would be only logical to expect progressive changes in the pigment epithelium of the retina and, as noted above, such a report was published recently.[12] A case of progressive retinopathy has been observed in a child with an immunoglobulin disorder.[31] Some evidence that the retinopathy may occur after naturally acquired rubella in early childhood was advanced by Franceschetti.[23] It is known that the virus may persist in the eye for periods as long as three years after birth, and perhaps longer. In the laboratory virus has been found in the retinal pigment epithelium of rats with the congenital rubella syndrome.[5] There is every reason to believe that it is present in the pigment epithelium of humans as well, proliferating and exerting its cytopathic effect from early fetal life. Later in gestation and after birth it may be accompanied by an inflammatory response affecting not only the retinal pigment epithelium, but also the underlying choroid.

In the literature there is no indication that the pigmentary variation changes in later life. Retinopathy has been observed in the Australian series in the second and third decade of life, and persists in those patients to the present.[46] This author, however, has not identified

rubella retinopathy in anyone in the fourth decade of life or older. Possibilities implicit in this suggestion, if it is true, are that rubella retinopathy is a new clinical manifestation of an old disease, or, more likely, that the retinopathy becomes less apparent with time and the maturation of the eye.

MICROPHTHALMUS

Microphthalmus and microcornea, often clinically inseparable, were found in 30 eyes in this investigation. Twenty-four of the eyes with microphthalmus or microcornea also had cataracts. Four of the 24 had glaucoma as well. One microphthalmic eye had glaucoma without cataract, 1 was associated with ptosis, 1 with optic atrophy, and 1 with retinopathy alone. Three of the patients with microphthalmic eyes are deceased. None was without other evidence of ocular congenital rubella. If accurate measurements had been possible in every case, many more eyes might have been considered microphthalmic. In this investigation, where median postoperative aphakic vision was 10/200, the coexistence of cataract and microphthalmus seemed to assure a poor postoperative visual result. Of the 30 eyes so recorded, 20 underwent cataract surgery. Four ended in phthisis. One had no light perception, 3 had light perception, and 3 had hand movements vision. Three saw 5/200, 5 were able to see 10/200, and 1 had 20/200 vision.

Vision in the remaining 10 eyes varied from no light perception to 20/60. Five of the children were so severely retarded that vision in their microphthalmic eyes could not be recorded.

Microphthalmus deserves special mention because of its frequency in congenital rubella.[27] Sometimes bilateral, often associated with cataract, it has been reported in 10 to 20 per cent of all children with the congenital rubella syndrome. It may be said to exist if the newborn eye is smaller than 16.5 mm in diameter. Since this measurement cannot be made accurately except by a pathologist measuring an enucleated eye, in clinical practice it is estimated. In fact the terms microcornea and microphthalmus are rather loosely confused so that, clinically, either or both is said to exist if the cornea measures less than 10 mm in diameter. It tends to be only moderate in degree in rubella, extreme microphthalmus being rare.[101] Presumably the virus induced delay in maturation and replication of the affected cells is responsible for microphthalmus and microcornea as it is on a larger scale for "failure to thrive."

While microphthalmus itself may not be a barrier to good acuity, associated retinal disorders in microphthalmic eyes, the coexistence of

nystagmus, and defects in the retina and optic nerve may combine to limit the acuity of such an eye. Only 3 of the 30 microphthalmic eyes reported here had vision of better than 20/100. The median vision of the aphakic eyes was hand movements vision. It is the clinical impression of more than one ophthalmic surgeon that there is apt to be more "trouble" with microphthalmic eyes after rubella cataract surgery.[37] Consequently we feel that microphthalmus is an important obstacle to good vision and presents a special problem in the management of congenital rubella cataract. Where it is associated with unilateral cataract it precludes the possibility of a satisfactory postoperative vision. Where it is associated with bilateral cataract it is a very poor prognostic sign.

NYSTAGMUS

Nystagmus was found in 42 of the children in this investigation. Usually found in association with cataracts and other forms of organic amblyopia, it was pendular or searching. Latent nystagmus, fine amplitude nystagmus, and jerk type nystagmus were also observed. Twenty-four of the patients with nystagmus also had cataract. The remainder were found in association with psychomotor retardation, glaucoma, strabismus, and retinopathy.

CORNEAL HAZE

Corneal haze (or corneal nebula) was found in 21 patients. It was observed to clear spontaneously in the first year of life in 3 patients. In the remaining 18 patients it persisted, always in associated with vision of 20/200 or less (Figures 8 and 9).

REFRACTIVE ERROR

Little note has been made of high refractive error as a significant part of the rubella syndrome although it seems to us that it is. Twenty children in this series had high hyperopia or high myopia, while 80 had refractive errors requiring the wearing of spectacles. In a normal population, according to Sorsby,[80] the mode of refractive errors in normal children between ages four and eight is +2.3 diopters.

Fifteen per cent of the normal population may have refractive errors greater than +3.5 diopters, 1.5 per cent greater than +5.5 diopters. Six of the children in this study had hyperopia with spherical equivalents ranging from +4.00 to +8.50. Two of the patients with spherical equivalents of +7.00 or more were amblyopic in the most hyperopic eye. Visual acuity in the other hyperopic eyes was not affected.

Myopia, on the other hand, according to Sorsby,[80] is uncommon, 1.5

per cent of children having −1.50 diopters or more of myopia. A myopia greater than −2.50 diopters is rare. Fourteen children in this study were found to have high myopia with spherical equivalents in both eyes ranging from −6.25 diopter to −25.00 diopters.

PSYCHOMOTOR RETARDATION

Psychomotor retardation has long been recognized as an important part of the expanded rubella syndrome. It affected 60 children in this series and presents the ophthalmologist with yet another problem in management. Most importantly the retarded intellectual and physical maturation of the child may affect his educational and social development. The Australian researchers have pointed out that initial gloomy prognostications concerning the intellectual potential of some of the rubella children were not always borne out and that many went on to make satisfactory social and intellectual adjustments in later life.[46] Unpublished data from psychometric evaluation of 173 of these rubella children at ages four to five revealed that only 71 had IQs of 90 or above, while 102 had IQs below that level. Forty-nine were frankly defective with IQs of less than 70.

STRABISMUS

Strabismus occurs in congenital rubella in three principal associations. With organic amblyopia, often found with microphthalmus, cataract, or glaucoma, strabismus is frequent. Where there is important psychomotor retardation, as in cerebral palsy, it is found in 60 per cent or more of patients.[30] Finally strabismus in children with the congenital rubella syndrome may occur naturally.

Fifty-eight of the 328 children developed strabismus at some time during their seven years of observation. Forty-one were esotropic and 17 were exotropic. As will be noted, a great number were associated with other ocular disorders.

Most reports in the literature allude to esotropia as the principal oculomotor deviation in the congenital rubella syndrome. Sometimes simply mechanical, more often sensory, it has been reported in from 40 to 60 per cent of congenital rubella children by the age of eighteen months.[61] High hyperopia, often in associated with microphthalmus, has been reported as a contributory factor. Cerebral palsy itself, notable for a high incidence of associated esotropia, is a frequent concomitant of the congenital rubella syndrome.[30] Unilateral amblyopia is a well known precursor of convergent strabismus. In this study 41 children were esotropic in greater or lesser degree, ranging from intermittent

esotropia through microstrabismus and accommodative esotropia to extreme degrees of constant "right angle" esotropia. Important obstacles to vision, i.e., cataract, corneal haze, and optic atrophy, among other ocular disorders associated with congenital rubella, were present in all but 11 of these patients.

Strabismic amblyopia was present in 4 of the children, 3 of whom experienced some improvement in vision after patching. Surgical correction of esotropia was attempted in 4 of the children. The results of strabismus surgery were unremarkable. Most of the children retained a degree of esotropia after surgery. None of the children with esotropia enjoys a significant degree of binocularity except for those 3 with intermittent esotropia who fused intermittently and had never developed amblyopia. The remaining 27 children who have been followed continue to be esotropic; 19 of them have amblyopic eyes with vision ranging from no light perception to 20/40; mean vision in the amblyopic eyes is 20/200.

The importance of exotropia as a part of the congenital rubella syndrome has been overlooked. Seventeen of the 58 strabismic patients developed exotropia in the first seven years of life; in 12 patients the exodeviation was seen in association with organic amblyopia. Only 5 of the 17 had normal visual acuity with constant alternating exotropia.

The incidence of strabismus in a normal population between birth and seven years of age is 4.5 per cent; of these 3.6 per cent are esotropic and 0.9 per cent exotropic.[25] In populations with lower intelligence quotients the incidence of strabismus, and especially the proportion of exotropia, increases. The 58 children with strabismus recorded here constituted 15 per cent of the total population, a figure that is consistent with that found in other populations with a high coincidence of psychomotor retardation. The ratio of 41 esotropes to 17 exotropes, or roughly 2.5 to 1, was within normal limits for such a defective population. However when considering only the strabismic children with no sensory obstacle to fusion, there were 11 children with esotropia and 5 children with exotropia. Thus the incidence of purely mechanical strabismus without sensory abnormality was not significantly different from that found in a normal population (not more than 5 per cent); but the relative incidence of exotropia (1.6 per cent) was almost twice that found in a normal population. It may be concluded that the incidence of strabismus in children with congenital rubella is four times that found in a normal population, but similar to that found in a population with a high proportion of psychomotor retardation. The strabismus was predominantly sensory (80 per cent); approximately 30 per cent of the

children with or without sensory disorder were exotropic. These figures are to be compared with a reported incidence of 20 per cent exotropia in a normal strabismic population[25] and previous clinical reports that virtually every strabismic rubella child is esotropic.[61]

PREGESTATIONAL AND LATE GESTATIONAL RUBELLA

Reference has been made earlier to children born of mothers who had acquired rubella from one to three months before pregnancy. We are aware of five in all. Two of these pregnancies resulted in abortion and two in early neonatal death. Only one survives. None of these abortuses or infants nor the surviving child demonstrated any evidence of ocular rubella. The author believes that this finding is coincidental, because preconception rubella tends to be unusually severe and other instances of preconception rubella with ocular damage have been reported.[27]

While most rubella embryopathy occurred in the first trimester of pregnancy, some of these changes followed maternal rubella later in pregnancy. In this series no patient with the expanded rubella syndrome was infected later than the thirteenth week of pregnancy. However 22 of the children infected after the first trimester were found to have some of the ocular stigmata of congenital rubella.

These clinical data which have been confirmed in the laboratory demonstrate the persistence of the rubella virus as an infectious agent. It is commonly believed that the period of viremia in adult rubella is very brief, yet in these five patients of whom we have knowledge, and those reported by others, it is clear that at least one episode of viremia must have occurred in the three months following clinical rubella infection. As for the continued teratogenic effect of virus in later pregnancy, the importance of such involvement has received little notice. These data, all confirmed in the laboratory, do not contradict Mann's dictum that the organ in process of most rapid development is most susceptible to the disruptive effects of viral infection.[44] In fact the preponderance of virus-induced organodysgenesis is in the very earliest months of pregnancy. These data do point out, however, that the developing fetus is susceptible to virus infection at any time during pregnancy and that important viral embryopathy may occur as a result of rubella infection late in gestation.

THE IMMUNE RESPONSE IN CONGENITAL RUBELLA

While we have presented an extensive prospective investigation of clinical congenital rubella in a large population, and have reviewed the description by others of the histopathology of congenital rubella, a

fuller comprehension of the syndrome is dependent upon an understanding of the immune responses of the fetus to the rubella virus. Clinical and laboratory data from this investigation outline clearly several distinct patterns of fetal immune response. It is these responses which dictate the course of the disease and define the clinical characteristics which we recognize as the congenital rubella syndrome. To this end, a brief review of the histopathogenesis of congenital rubella is appropriate here.

HISTOPATHOGENESIS

Once established in the developing fetus, as was described earlier, intracellular virus slows the replication of the fetal cell, often to half the normal rate. Mann[44] has observed that the immature cell in process of most rapid development is particularly susceptible to the cytopathic effect of viral invasion. Where early infection is severe but consistent with life, the morbidity of the virus is likely to result in the so-called expanded congenital rubella syndrome, with ocular, auditory, cardiac, mental, reticuloendothelial, osseous, dental, and cerebral involvements. However such extensive and devastating evidence of viral infection is found only in early gestational rubella during the period of most rapid fetal development and critical organogenesis.

Infection later in pregnancy, after much of the critical organogenesis has been accomplished, is inclined to be less devastating to the developing fetus, still slowing the rate of cellular replication and growth but without many of the teratogenic effects that characterize early gestational rubella. Indeed the histopathogenesis of later gestational rubella is principally inflammatory, presumably evoked by the immune response of the fetus to circulating virus, viral antigens, and virions. Thus one disease agent can produce two distinctly different fetal diseases: an early gestational teratogenic disease, and a late gestational inflammatory disease.

THE ORIGINS OF THE IMMUNE RESPONSE

The fetus suffering from congenital rubella may develop several patterns of immunity. It was once considered axiomatic that no newborn was immunologically competent, that fetal circulating antibody was acquired transplacentally, and that until age four to six months after birth the immunologic status of the newborn simply reflected that of his mother. It is now recognized, however, that the only maternal antibody capable of being transmitted transplacentally is 7S-IgG globulin.[10,4]

More recent information, brought into sharper focus by the study of

prenatal viremias such as rubella and cytomegalic inclusion disease, has demonstrated that the fetus may, in fact, have an immune response to foreign antigen almost as soon as there is sufficient mesenchymal differentiation to permit the formation of antibodies.[58,78,51] Though the development of immune competence is uneven and difficult to place in time, it seems likely that such a response in humans is at least theoretically possible toward the end of the first trimester of pregnancy.[82] This is not to say, however, that the fetus develops instant immunological competence. Evidence in fetal monkeys points to gradual development of immune response to antigenic stimuli over a period of time, starting in early fetal life and lasting well into the first years of postnatal life.[82] Neutralizing antibody has been found in rubella fetuses as early as the sixteenth week of gestation,[78] and hemagglutination inhibition antibody (HI) has been found in fetuses shortly thereafter in the twentieth week of pregnancy.[78] However the function of such antibody is not clear. At least one of the antibodies (IgA) is apparently unable to influence the replication of the virus.[4] Further it is not established that any of the antibodies at this stage is capable of effectively neutralizing the rubella antigen or modifying its infectivity or mediating its disposal.[31]

An important discrepancy exists here. It is clear from the foregoing that some form of fetal imunological competence may exist as early as the fourth month of fetal life. Tondüry, on the other hand, states categorically that fetal inflammatory response does not exist before the seventh month of gestation.[88]

THE CHRONOLOGY OF THE IMMUNE RESPONSE

Host response to prenatal viral infection may be considered chronologically. We have seen that before the development of a recognizable mesoderm the fetus can have no immunity of its own. The beginnings of the immune response probably occur at three to four months of fetal age.[82,18] At birth the rubella baby has levels of neutralizing hemagglutination inhibiting (HI), and complement fixing (CF) antibody which as a rule are not significantly different from maternal levels.[1] As in normal infants, levels of CF antibody decline in the first months of life while other serum antibody levels persist, presumably for life.[51] Persistence of antibody beyond six months of age is generally indicative of congenital infection. A significant number of rubella infants in this investigation, however, demonstrated rapidly falling antibody titres so that, at age one, 20 per cent of the children had very much diminished levels of serum antibody and 10 per cent had no detectable level at all.[32] When challenged with rubella antigen in later life, either by vaccina-

tion or natural exposure, many congenital rubella children may demonstrate a rise in serum antibody but not to the level one would expect; furthermore the elevation of serum antibody may be transient.[38] Kenrick found that 20 per cent of congenital rubella children go on to acquire rubella later in life.[40] Menser reported that one of Gregg's original rubella children acquired rubella herself during a pregnancy and produced a child affected by congenital rubella.[49] In this investigation one congenitally infected child acquired rubella just before his fifth birthday. Partially deaf before the acquired infection, he became profoundly deaf after it.

PATTERNS OF IMMUNITY

Thus, from before birth and into early childhood, 80 per cent of congenital rubella children will demonstrate levels of serum antibody consistent with congenital infection. Twenty per cent of congenital rubella children have declining levels of rubella antibody. While the normal function of antibody is the neutralization of antigen, it is not clear that the antibody in congenital rubella infection is able to perform that function effectively,[11,40,58,45] Virus may be isolated from the excreta of many congenital rubella children while they possess high levels of rubella antibody, and no evidence of a systemic inflammatory response to the rubella virus.[32] Of the various patterns of immunity that may explain the existence of high levels of antibody in a congenital rubella child who is actively shedding virus, several deserve mention.

First, the fetus infected in the first trimester may develop immune tolerance for the virus, i.e., failure to recognize the virus as "non-self." It is possible that such immune tolerance may continue through gestation and into postnatal life. While the importance of such a non-response is disputed, there is no doubt that it can exist and there is solid laboratory evidence to demonstrate the absence of antibody in some infants who are actively shedding rubella virus in the nasopharynx, the eye, the cerebrospinal fiuid, the urine, and the feces.[32]

Second, as noted above, the fetus is capable at, or before, the fifth month of gestation, of developing antibody to viral antigen. Neutralizing, hemaggultination inhibiting, and complement fixing antibody have all been demonstrated in fetuses at the fifth month of gestation and regularly in newborn rubella babies.[1,51,96] The titers may be less than those found in individuals acquiring rubella naturally in later life and are sometimes so low as to suggest the existence of an immunoparesis.

Immunoparesis, as its name implies, defines a condition in which the production of antibody in comparison to the severity of the infection is

disproportionately low. There is no laboratory evidence to suggest that the quality of the immune globulin is affected, although, as pointed out above, it is difficult to know why antibody stimulated by a specific antigen would apparently have no effect on that antigen in vivo. Studies, incomplete at this time, indicate that immunoparesis may reflect viral interference in the normal production of immunoglobulins and may be proportional to the severity and inversely proportional to the duration of the rubella infection.[18,31,57,11,58] Tending to disappear in infancy, as the virus levels decrease and imunologic competence increases, the immunoparesis is generally uneven, delaying the development of antibody to some antigens, but not to others.[82] For example, the production of IgM antibody, normally low at birth and rising in the first year of life, tends to remain low; and the development of IgG antibody in the first year of life may be delayed.[51] Similarly lymphocytes in congenital rubella may be unresponsive to some antigenic challenges (phytohemagglutination, for example) while remaining resistant to infection with rubella virus.[59]

The role played by interferon (IF) in host resistance to rubella virus infection is not altogether understood. While efforts have been made to draw clinical conclusions from in vitro studies of interferon, some caution must be exercised in their interpretation. Several conclusions, however, seem justified.

Interferon is a major determinant in recovery from virus infection.[18] Produced in the infected organ as well as in the reticuloendothelial system, it acts intracellularly to halt not only the replication of the virus locally but also its extracellular spread. The interferon protected cell replicates more slowly than normal. Interferon virus reaction within the cell may lead to cellular death.[56] Interferons are not virus specific; one virus may produce many interferons and one interferon may be produced by a number of viruses. In the chronology of viral infection the production of interferon is probably one of the earliest evidences of host resistance.[3] Rubella virus is known to be exquisitely sensitive to interferon.[50]

The production of interferon in cases of congenital rubella is stated to be unaffected. Determination of interferon levels in 65 of 68 sera from 16 children in this investigation were found to be within normal limits. Interferon levels in 3 of the sera from the same 16 children were minimally elevated.

The importance of sex as a factor in the immune response to prenatal viral infection has been brought out recently. Male fetuses and infants are more likely than females to excrete virus for very long periods.[92]

Such differences cannot be ascribed to steroid hormone metabolism since in early life there is little difference in the production of such hormones in male and female infants. In most series male infants tend to be more severely affected and show more evidence of viral disturbance of normal growth patterns in early life. In this investigation of congenital ocular rubella sex-related differences could not be documented. Thirty of 54 patients with cataracts were female, as were 36 of 78 patients with retinopathy, and 17 of 30 children with microphthalmus.

CONGENITAL RUBELLA, AN IMMUNOPARETIC INFLAMMATORY DISEASE

As we have reiterated, congenital rubella early in pregnancy is notable for the organodysgenetic effects of virus infection. Only in later gestation, infancy, and childhood are the inflammatory effects of rubella virus manifest. Reference has been made to the clinical observation of iritis.[41] In other organ systems arteritis and encephalitis are among the many evidences of the inflammatory nature of rubella virus infection in late gestation.[52] The ophthalmic pathologists have underlined the prevalence of inflammatory infiltration of the uvea seen in "almost every case" of ocular rubella that was studied.[101]

Scheie and associates [73–75,97] as noted above, presented a number of well documented cases in which the ocular morbidity following extraction of rubella cataracts at an early age was very high; 55 per cent of the eyes developed important postoperative complications when operated before age one, compared with 5 per cent in uncomplicated congenital cataracts. They implicated the release of intralenticular virus in the eye as a cause of postoperative iridocyclitis which was sometimes severe enough to lead to phthisis. Boniuk and Zimmerman,[6,7,100] among others, have pointed out the frequency with which evidence of iritis is found in rubella eyes. In Scheie's opinion[74] opening the lens capsule and releasing virus into the eye may aggravate a pre-existing inflammation, producing the morbid results which he was reported.

Postoperative inflammation and phthisis bulbi are common to all series of rubella cataract operations reported but not in the numbers that Scheie recorded, causing one to look for other factors involved. Von Noorden et al. have reported only 2 of 36 eyes with severe postoperative inflammation leading to phthisis,[9] Parks 1 of 24 eyes,[64] Hertzberg 2 of 80 eyes,[37] and Boniuk and Boniuk 4 of 76 eyes.[8] It is of interest that Scheie performs a preliminary iridectomy and, in a separate procedure three or four weeks later, aspirates the lens. At least one of Scheie's eyes was lost to phthisis after the iridectomy and before the lens was operated.[74] Both of Hertzberg's cases leading to phthisis followed the

same pattern: a severe inflammation following the preliminary iridectomy. Both eyes were lost before an attempt could be made to aspirate the lens.[87] Clearly the inference is that the iridectomy may be coresponsible with lens aspiration for the postoperative inflammation, even though the iris yields positive virus cultures in only 12.5 per cent of cases as opposed to 47 per cent in the case of the lens. Perhaps, as Cordes pointed out, there is less morbidity in congenital cataract surgery if the procedure can be performed in a single stage.[17]

It has been suggested that the incidence of important postoperative inflammation and phthisis bulbi is greater at an early age and that cataract surgery should be delayed until one year of age, or later.[75] Four of 68 eyes reported here became phthisical after cataract surgery. One was operated at three months, one at six months, one at eighteen months, and one at four years.

Factors other than age at operation, i.e., the number of surgical procedures performed, may play a role in the development of phthisis. We have noted the ample evidence that the rubella eye is the site of a chronic viral iridocyclitis and that up to three years of age, and perhaps longer, any part of the eye including the lens may harbor live virus.[48] The hazards of operating on an inflamed eye are known to every ophthalmic surgeon, as are the hazards of multiple operative procedures on the same eye. It has been suggested that the profound inflammation following surgery is an immune response of the delayed hypersensitivity type predicated on repeated sensitization of the eye to viral antigen and culminating in a massive viral insult when the lens capsule is opened at the time of cataract surgery.[97]

Our investigations have pointed up a number of similarities in the immunological patterns of those 7 children who developed phthisis bulbi. In 6 of the children the eye that went on to become phthisical was microphthalmic. Virus was cultured from 5 of the 6 children, in 3 instances from the eye.

Two of the 7 patients showed no detectable level of HI antibodies. Three patients had low or steeply declining levels of HI antibodies, 2 reaching undetectable levels. Two patients sustained moderately elevated levels of HI antibody.

Reference has been made to the immunological competence of the fetus during gestation, at birth, and in the early years of life. Those children who manifested immunologic tolerance to the virus would not be expected to respond to increased exposure to virus in any way. Those who demonstrated a degree of immunoparesis with low levels of humoral or tissue-fixed antibody should not reasonably be expected to

respond to increased exposure to virus by developing severe intraocular inflammation. However they might respond normally to another antigen, lens protein, for example. Evidence that surgery is followed by a period of immunosuppression lasting from one to several weeks has been published recently.[62] Children in this investigation with high levels of rubella antibody at birth frequently were observed to have declining titers in the first month of life. Whether this was a reflection of immunoparesis, or of declining levels of rubella virus in the system, or of declining levels of maternal antibody (IgG) combined with inability of the infant to generate his own, is not known. When such children in later life are challenged with rubella antigen, their response is often feeble, with diminished elevation of circulating antibody levels; 20 per cent have no apparent immunity to rubella infection of any kind.[32,40]

Other factors may play a part, such as interferon, about which little is understood in this context.

RUBELLA VACCINATION

Whatever knowledge we have of the rubella virus – its characteristics, the epidemiology of rubella virus infection, and the patterns of immunity it evokes – can all be traced back to the isolation of the rubella virus in the laboratory. The same can be said of rubella vaccination which, in preventing recurrences of periodic rubella epidemics, offers the best hope for "cure" of the congenital rubella syndrome.

Immunity to rubella, acquired by all but 2 per cent of immunologically competent individuals, is stated to be "lifelong and solid." While from time to time and place to place there is some variability in the percentage of rubella immunes in the population, the figures varying from 15 per cent to 92 per cent, a reasonable estimate is that half of the population is immune at age ten, 85 per cent by age forty.[79] Judging by the presence of serum-neutralizing antibodies in standard populations in the continental United States, it is likely that 15 to 30 per cent of females in the childbearing age are susceptible to infection by rubella virus.[79] Serologic tests for immunity include most reliably the determination of hemagglutination inhibiting antibody (HI).[1] Determinations of complement fixing antibody (CF) and of the various neutralizing antibodies (IgA, IgM, IgG) are also performed. While a higher titer of HI antibody in a single specimen is suggestive, the discovery of a fourfold or greater rise in antibody titer in examinations of paired sera of individuals suspected of having been exposed to rubella makes the diagnosis of recent infection secure. HI antibody is the accepted stan-

dard determination and is available in most state laboratories. The finding of IgM globulin in the serum, a test not so often or easily performed, indicates infection within the past three or four weeks.[102]

Without a doubt the best immunity is that provided by the naturally acquired disease. Several strains of rubella vaccine have developed, all of which produce measurable levels of antibody in the vaccinated individual. Antibody titers following vaccination, however, tend to be lower than in naturally acquired disease and may not persist.[40] In one study 100 per cent of the vaccinees developed rises in antibody titers when challenged with "wild" rubella virus, although none acquired the clinical disease.[38] It is likely that rubella vaccination does not completely protect against subsequent reinfection. At the time of this writing the attenuated virus has been recovered from the placentas of three pregnant vaccinees, and there is one instance of maternal vaccination having produced congenital rubella (without ocular stigmata) in a fetus.[90] There are no known instances in which a pregnant vaccinee has acquired natural rubella and produced a child with the congenital rubella syndrone although, as noted above, it is theoretically possible. The periodicity of rubella epidemics suggests that 1970 and 1971 might have been years in which a rubella epidemic could have been anticipated. That no epidemic occurred may speak to the efficacy of programs which have vaccinated 25 million children in large American communities.

Gamma globulin probably has no part in the treatment of rubella in mother or child, nor does it seem to have any effect on the course of the disease or the likelihood of its transmission across the placenta. It may, however, diminish virus shedding and also alter maternal seroconversion.[51,20]

SUMMARY AND CONCLUSIONS

This is the only long-term prospective investigation of the ocular manifestations of congenital rubella emanating from the widespread American epidemic of 1963–4. It is based on observations of 328 children, many of whom have been followed from the time of their mother's registration in the prenatal clinic to the child's seventh birthday. In every child the diagnosis of congenital rubella has been confirmed in the laboratory. One hundred and seventy-five children have had at least one of the ocular stigmata of congenital rubella. Eliminating those children who were referred to the investigation after the diagnosis of ocular rubella had been made, it is estimated that ocular involvement occurs in 42.5 per cent of children with clinical evidence of congenital rubella.

The histopathology of the congenital rubella syndrome, as described by others, has been reviewed. The incidence of ocular defects ocurring as a result of rubella embryopathy has been summarized. Fifty-four patients with rubella cataracts have been followed from birth. Vision following rubella catract surgery is generally poor, the mean vision being 10/200. At seven years of age the vision in those patients operated upon before one year of age is not significantly different from vision in those operated upon after one year of age. Severe postoperative inflammation, leading to phthisis bulbi, has been found in 4 of 68 eyes operated upon for congenital rubella cataract.

Glaucoma in congenital rubella, found in 15 cases, tends to be severe, with 8 of the 15 children blind at seven years of age. Buphthalmos is a frequent concomitant of congenital rubella glaucoma. Corneal haze has been observed in 11 of the 15 cases and tends not to clear with age. The relationship between cataract and glaucoma has been explored and the two conditions found to occur together at the same statistical frequency at which occurs independently in a population of children with ocular evidence of congenital rubella.

Retinopathy has been observed in 78 patients. In 9 it was absent or non-apparent in early life, becoming more obvious at time of later examination, suggesting that the retinopathy of rubella is progressive. In six patients it is associated with vision of 20/40 or less in the affected eye or eyes.

Strabismus is reported in 58 patients, 17 of whom are exotropic. The incidence of strabismus in congenital rubella is four times that found in a normal population. The incidence of exotropia is six times that found in a normal population. Important obstacles to vision, i.e., cataract, optic atrophy, corneal haze, and other ocular disorders associated with congenital rubella occurring in 42 of the 58 patients, play a major etiological role in the strabismus of congenital rubella.

Extremes of refractive error have been observed in 20 patients. Fourteen children have myopic refractive errors of −6.25 diopters or greater. Psychomotor retardation is found in a high proportion of the children described here.

Pregestational and late gestational rubella infection is discussed. One patient with preconception congenital rubella is reported. Twenty-one patients with late gestational congenital ocular rubella are reported, some of whom were infected as late as the eighth month of fetal life.

Patterns of immunity in congenital rubella are seen in the context of the development of immunological competence in the fetus. The importance of the early teratogenic and ontodysgenic effects of rubella virus in the fetus is emphasized. The discrepancy between the develop-

ment of fetal antibody at the fourth month of fetal age and the first evidence of fetal inflammatory response occurring at the seventh month of fetal age has been pointed out and possible explanations offered. We have suggested that the development of immune competence is gradual, beginning at conception with the immune null state and progressing through immune tolerance and immunoparesis to a modified adult immunity, a condition which persists for life. Viral interference with the lymphoreticular antecedents of immunological competence has been implicated, a theory supported here by the relative immunological incompetence of many of those children affected earliest and most severely by congenital rubella. Against this background the postoperative development of severe inflammation leading to phthisis bulbi is seen not as a delayed hypersensitivity response to intraocular virus, but as a non-specific response to surgical trauma occurring in a chronically inflamed eye. Seven eyes with severe postoperative inflammation leading to phthisis bulbi have been described. In four eyes phthisis occurred after cataract surgery, in one aphakic eye after glaucoma surgery, in one eye after detachment surgery, and in one eye after a conjunctival flap had been pulled over a corneal ulcer. Six of the seven eyes were microphthalmic. The virus was isolated from five of the seven patients with phthisical eyes. Five of the seven patients had initially low or falling hemagglutination inhibition titers, suggesting the existence of immunological paresis.

Finally the current status of rubella vaccination has been discussed. While the duration and efficacy of attenuated rubella virus vaccination are not proven, it is seen as the best preventive "cure" for the congenital rubella syndrome.

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