THE OCULAR MANIFESTATIONS OF CONGENITAL INFECTION: A STUDY OF THE EARLY EFFECT AND LONG-TERM OUTCOME OF MATERNALLY TRANSMITTED RUBELLA AND TOXOPLASMOSIS

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ABSTRACT

Purpose: To study the spectrum of adverse ocular effects which result from maternally transmitted rubella and toxoplasma infection; further, to record the long-term visual and neurodevelopmental outcomes of these 2 major causes of fetal infection.

Study Design and Patients: A series of 55 patients with congenital infection have been studied prospectively on a long-term basis. The study group included a cohort of 34 cases with congenital rubella syndrome demonstrated by virus isolation, and 21 cases with a clinical diagnosis of congenital toxoplasmosis and serologic confirmation. All patients had specific disease-related ocular defects. Rubella patients were first identified during or following the last major rubella epidemic in 1963-1964, and some have been followed serially since that time. A separate study group of representative toxoplasmosis patients presented for examination and diagnosis at varying time periods between 1967 and 1991.

Observations and Results: This study confirms that a broad spectrum of fetal injury may result from intrauterine infection and that both persistent and delayed-onset effects may continue or occur as late as 30 years after original infection. Many factors contribute to the varied outcome of prenatal infection, the 2 most important being the presence of maternal immunity during early gestation and the stage of gestation during which fetal exposure occurs in a nonimmune mother.

Rubella: As a criteria of inclusion, all 34 rubella patients in this study exhibited one or more ocular defects at the time of birth or in the immediate neonatal period. Cataracts were present in 29 (85%) of the 34, of which 21 (63%) were bilateral. Microphthalmia, the next most frequent defect, was present in 28 (82%) of the 34 infants and was bilateral in 22 (65%). Glaucoma was recorded in 11 cases (29%) and presented either as a transient occurence with early cloudy cornea in microphthalmic eyes (4 patients), as the infantile type with progressive buphthalmos (1 patient), or as a later-onset, aphakic glaucoma many months or years following cataract

aspiration in 11 eyes of 6 patients. Rubella retinopathy was present in the majority of patients, although an accurate estimate of its incidence or laterality was not possible because of the frequency of cataracts and nystagmus and the difficulty in obtaining adequate fundus examination.

Toxoplasmosis: Twenty-one patients with congenital toxoplasmosis have been examined and followed for varying time periods, 7 for 20 years or more. The major reason for initial examination was parental awareness of an ocular deviation. Twelve children (57%) presented between the ages of 3 months and 4 years with an initial diagnosis of strabismus, 9 of whom had minor complaints or were diagnosed as part of routine examinations. All cases in this study have had evidence of retinochoriditis, the primary ocular pathology of congenital toxoplasmosis. Two patients had chronic and recurrent inflammation with progressive vitreal traction bands, retinal detachments, and bilateral blindness.

Macular lesions were always associated with central vision loss; however, over a period of years visual acuity gradually improved in several patients. Individuals with more severe ocular involvement were also afflicted with the most extensive central nervous system deficits, which occurred following exposure during the earliest weeks of gestation.

Conclusions: Although congenital infection due to rubella virus has been almost completely eradicated in the United States, the long-term survivors from the prevaccination period continue to experience major complications from their early ocular and cerebral defects. They may be afflicted by the persistence of virus in their affected organs and the development of late manifestations of their congenital infection.

Congenital toxoplasmosis continues to be the source of major defects for 3,000 to 4,100 infants in the United States each year; the spectrum of defects is wide and may vary from blindness and severe mental retardation to minor retinochoroidal lesions of little consequence. Effective solutions for either the prevention or treatment of congenital toxoplasmosis have not been developed in this country but are under intensive and continuing investigation.

INTRODUCTION

Many agents have been implicated as having an adverse effect on fetal development and causing ocular abnormalities. In addition to chemicals, drugs, alcohol, and nutritional substances, microorganisms have long been known to cross the placental barrier and cause fetal infection. A direct relationship between specific ocular and systemic abnormalities in the newborn and maternal infection was first noted and recorded by an Australian ophthalmologist, Gregg, in 1941.[1] His observations provided

the first record of the teratogenic effect of viral infection, and numerous organisms have been convincingly demonstrated to cause fetal malformations and disease since that time.[2-5]

Although there have been major accomplishments in the eradication and control of infectious disease through the availability of immunization programs, antibiotic therapy, and effective public health measures, congenital infection continues to be an extremely important cause of fetal morbidity and mortality. The number of affected pregnancies can only be estimated, since early exposure and overwhelming infection will often be incompatible with life, and the products of conception may undergo resorption or result in spontaneous abortion or stillbirth. The majority of infants born to mothers with documented prenatal infection are *asymptomatic* at birth; however, a smaller number who are infected early in gestation by rubella virus or toxoplasma organisms will be *symptomatic* and have visible evidence of malformation, tissue destruction, or chronic disease early in the neonatal period. It is a paradox of nature that during this unique period when the developing fetus (in utero) should be in its most protected environment, it may actually be most vulnerable, lacking its own immune defenses or any immunologic protection from a nonimmune mother.

These 2 infectious diseases, rubella and toxoplasmosis, one a virus and the other a protozoa, each cause only a mild and relatively benign, short-term illness as an acquired infection in an adult. When these organisms are passed from an infected mother transplacentally in utero, however, the developing fetus may suffer serious injury. Together, these organisms provide a comprehensive insight into the transmission, pathogenesis, and disastrous effects that have become known as congenital infection, or the congenital infection syndromes.

Each organism has a unique pathogenetic process with different target tissues in the eye; rubella infection early in gestation causes a high incidence of cataracts and generalized infection,[1,6-12] whereas early infection by toxoplasma organisms causes major areas of focal necrosis of the retina and brain.[13-16]

Rubella has been one of the most extensively studied, thoroughly researched, and best understood microorganism in recent history. Its virtual eradication in populations with effective and universal immunization programs is a major achievement of medical science. The last major rubella epidemic in 1963 to 1964 resulted in approximately 12.5 million cases of clinically acquired rubella in the United States and seriously affected more than 30,000 infants, with more than 13,000 fetal or early infant deaths and 20,000 infants born with major congenital defects.[7,9] The eventual cost of that epidemic has been estimated at more than $2 billion.[17,18]

A positive outcome of those disastrous postepidemic years was a peri-

od of intense investigation of rubella virus and its role as a human pathogen. Those clinical and virologic studies demonstrated rubella virus to be an ideal model to illustrate the pathogenesis of fetal infection and the routes by which microorganisms may be transmitted from maternal to fetal systems. Our understanding of the complex mechanisms that account for fetal malformations was expanded, and a new concept of chronic fetal infection involving both the persistence and shedding of viable organisms through the neonatal period was revealed. These infants were found to harbor and shed virus for many months and, in some instances, years afterward.[6-12,19-22]

Toxoplasmosis continues to be a major cause of congenital infection with significant fetal morbidity and is also recognized as the single most important infectious cause of retinochoroiditis in the United States.[23-27] Although active inflammation may be present at any time through the pediatric, adolescent, or adult years, with few exceptions, such episodes of infection are generally considered to be recurrence of congenital toxoplasmic infection.[24] Effective measures to prevent and treat toxoplasmosis in humans are a source of intensive investigation.

This descriptive study reports long-term observations on 55 individuals documented with congenital infection caused by either rubella or toxoplasmosis with particular reference to their ocular and neurodevelopmental status.

HISTORICAL BACKGROUND

Observations of human malformations precede written history; their occurrence was often associated with religious symbolism and attributed to "evil spirits." Clay tablets from Nineva, which record an earlier period prior to 2000 BC, depicted some 62 forms of human malformation, many of which might be recognizable today.[28] Through the centuries, the causes of congenital deformities remained mostly in the realm of superstition, religion, and folklore. The first to recognize a scientific basis for fetal malformations was William Harvey (1651), who, using cleft palate and harelip as examples, traced the development of the fetus from the egg and suggested that congenital deformities arose as an "arrest of development" of specific tissues at a particular stage.[28]

The general theories of causation of birth defects had long centered on the vague concepts of "faulty germ plasm" and the effect of "noxious agents." The idea that contagious infection might be transferred by minute, invisible particles was first expressed by Fracastoro in 1546. This "germ theory" was developed much later in 1855 by Snow, who argued that the causative agent of cholera was a living cell that multiplied with great rapidity but was too small to be seen under the microscopes then in use.[29] It was in 1867 that

Virchow was credited with the observation that maternal infections may be transferred to the fetus either through the placental circulation or the amniotic fluid and that the diseases or defects of the infant may differ in expression or location from that of the acquired adult infection.[28]

Ophthalmology can be justly proud of its participation in the gradual exposition of congenital infection as a cause of abnormalities in the developing infant and as a specific cause of ocular malformations and disease. Much of our knowledge of congenital abnormalities has been attributed to "the painstaking records of clinical observers who have collected vast numbers of examples of all kinds of malformations."[30] Such efforts by clinicians have allowed abnormalities to no longer be thought of as entirely fortuitous and meaningless, but as a source of essential information and opportunity to investigate and understand their causes.

Two ophthalmologists made major contributions to our knowledge of the epidemiology, pathogenesis, and clinical course of fetal disease. Most important were the observations of Gregg,[1] who was the first to present conclusive evidence of the teratogenic effect of a virus. He proposed the new concept that maternally transmitted infection could have extensive damaging effects involving multiple organ systems of the developing fetus. His lucid descriptions of the ocular and systemic defects of rubella remain a classic in ophthalmology and a milestone in medical epidemiology.

Earlier, in 1923, a Czech ophthalmologist, Janku, recorded observations that proved to be extremely important to our understanding of the toxoplasma organism as a fetal pathogen. He found parasitic cysts in the retina of an 11-month-old child with congenital hydrocephalus and "colobomas of the macular area"; however, the organism was not conclusively identified as *Toxoplasma gondii* until 1928.[31,32] Working independently, Splendore in Brazil observed toxoplasma organisms in the rabbit, and Nicolle and Manceaux in North Africa found the protozoa in the spleen and liver of an African rodent, the gondi. They derived the name *Toxoplasma gondii* from the Greek word *toxon* meaning a bow or arc, which is the most striking feature of the proliferative form of the organism.[23,32]

Clinical observations and reports such as those of Gregg and Janku have received great praise " . . . as excellent examples of how epidemiologic observation may be important in unraveling the etiology of some diseases and morbid conditions. They also serve to remind us that although advances have been increasingly based on laboratory research, the observation and recording of naturally occurring events still holds a time-honored place as a significant method of research."[33]

RUBELLA

Following the early descriptions by 2 German physicians, de Bergen in

1752 and Orlow in 1758, the disease became known colloquially as German measles. These investigators gave the first clinical descriptions of this acute exanthem as a separate entity and gave it the German name "Rötheln," which was used for many years. In 1815, Maton further detailed the clinical characteristics, and in 1866 the Scottish physician Veale described 30 cases. Considering the term "Rötheln" to be "harsh and foreign," he introduced *rubella* as a "short and euphonious name." Since that time, "rubella" has been generally accepted but is frequently interchanged with "German measles."[17,34,35]

Gregg's observations in 1941 were actually published as "Congenital cataract following German measles in the mother" and made a major impact forever on the importance of this mild infectious disease of childhood.[1] Gregg, as an ophthalmologist, noted several infants with cataracts having an unusual appearance that was not common to his experience. The story is related of the serendipitous presence of 3 mothers in his office waiting room with infants having cataracts. They discussed their pregnancies and noted the coincidental early measles infection each had experienced, information which they shared with their doctor.[34] Over a period of months Gregg examined 10 additional infants with similar cataracts, noting many to be small and sickly babies and often with small eyes. With his peers he ultimately gathered a total of 78 cases, confirming the association that these were babies born of mothers who had rubella during the early stages of their pregnancies.[1] Within 2 years the epidemiologist Swan and his colleagues confirmed and expanded Gregg's observations, recording the major associations of congenital heart disease, cataracts, deafness, the frequent presence of low birth weight, failure to thrive, and signs of meningitis with central nervous system damage.[6] A quarter century elapsed before the isolation and identification of rubella as a virus and as the specific organism responsible for both a mild exanthematous disease and the devastating effects of intrauterine infection on the fetus.[6-12]

The rubella epidemics of 1963-1964 produced thousands of afflicted infants and, although tragic, did enable investigators to observe and confirm for the first time the pathogenic chronology of maternally transmitted infection, utilizing scientific methods that had never previously been possible. That fetal malformations and defects could result from early gestational infection was well known. These infants, however, exhibited manifestations of fetal infection never previously recognized: the presence of chronic disease in the newborn. They not only had active meningoencephalitis and liver and spleen enlargement, but also harbored live virus in almost every bodily organ and actively shed viruses in most bodily fluids and secretions. The magnitude and severity of fetal injury observed through this period motivated extensive study of the natural history of rubella, and a large-scale effort was made to prevent infection through the

development of an effective vaccine and immunization program. The first vaccine was licensed in the United States in 1969, and reduction in congenital infection from rubella has been both dramatic and long-standing.[17,33,36]

TOXOPLASMOSIS

The protozoa *T gondii* was first recognized as a cause of disease in animals and continues to be a concern as a cause of abortion in sheep and swine in certain countries.[32] Following the early report by Janku, it was not until 1939 that Wolf and associates in a series of studies identified *T gondii* first as a cause of infantile encephalitis and later documented the protozoa as a cause of maternally transmitted fetal infection and disease.[37] The primary diagnostic serologic test, the dye test, was developed by Sabin and Feldman in 1948.[38] This enabled investigators to study the clinical aspects of toxoplasmosis and to demonstrate that the organism *T gondii* was, in fact, the cause of widespread human infection. Several ophthalmologists have been prominent in research and clinical investigation of toxoplasma as a major cause of ocular infection, particularly of the retina. Hogan, Kimura, and O'Connor have made numerous contributions in this area [13-15] Wilder's observations of toxoplasma organisms in a series of cases of posterior uveitis thought originally to have been mainly due to tuberculosis provided a major breakthrough in our knowledge of toxoplasma as a cause of retinal disease.[16] The studies of Perkins[24] constitute a major contribution to our understanding of congenital retinochoroiditis and the concept that with few exceptions active retinochoroiditis, recurrent satellite lesions, or old, healed, inactive retinal lesions are all manifestations of congenital infection. Review of current literature is noteworthy for the innumerable studies, reports, and laboratory contributions of Remington and coworkers in the United States, Desmonts and coworkers in France, and the Chicago Toxoplasmosis Study Group directed by McLeod.[2,27,32,39-42]

STUDY DESIGN, PATIENTS, AND METHOD

This study consists of prospective observations of 2 separate patient populations, each consisting of individuals with ocular defects and congenital infection demonstrated by culture or serologic methods. A total of 55 cases is included.

THE RUBELLA COHORT

The rubella cohort is made up of 34 patients with congenital rubella syndrome (CRS). This term is used to denote the almost universal presence of rubella-assocaited abnormalities when ocular defects are present. The major portion of the CRS, or rubella, group was recruited in 1965 as part

of a personal research project in conjunction with the Perinatal Research Branch of the National Institutes of Health. Twenty infants with ocular defects were documented to have rubella by virus isolation from a total study population of 45 infants. Recovery sites included conjunctiva, throat, aqueous, iris, and lens. Other individuals in this continuing series were also identified as CRS infants during the same period. Based on their recruitment and follow-up in either private ophthalmologic offices or in the clinic service of what was then named The Children's Hospital of the District of Columbia, they are divided into 2 separate groups and designated as "private cases" or "clinic cases." Sixteen infants are included in the former and 18 in the latter hospital-based clinic source. Several cases were added from other ophthalmologic practices during that postepidemic period. It is to be noted that inclusion in the study group required both the presence of an identifiable ocular defect and a positive diagnosis of rubella by virus isolation or serologic confirmation.

TOXOPLASMA GROUP

The second patient population consists of 21 individuals with clinical evidence and serologic confirmation of congenital toxoplasmosis. In the majority of cases, serologic confirmation in the mothers was also obtained. These patients have been included in the study group on a consecutive basis with the earliest recruited and examined in 1965. Individuals with combined diagnoses (eg, toxoplasma and HIV or toxoplasma and CMV) have been excluded from this study group. Some individuals have been followed for the entire period and others added as their disease process was identified.

METHOD

A roster of patients from the 1965 rubella study that had been maintained were carefully reviewed and all available survivors reexamined. Some cases have been followed on a consecutive basis by the author, associates, or peers for as long as 32 years. Since the majority of these patients had been hospitalized at least one time at the same children's hospital, it was possible to retrieve and review the archival records. Clinical records were easily available for those patients still under care. A significant number of individuals in the "clinic patient" population, however, were either deceased or "lost to follow-up." This is thought to be at least partially due to the multi-handicapped status of these children and the frequent disruption in their family lives. There was a significant incidence of psychomotor retardation and cardiac disease among children in this rubella group, and it is presumed that many of them are deceased.

A greater number of the "toxoplasma patients" have been available to follow-up for longer periods of time. Their records have been reviewed,

the patients reexamined, serologies repeated, and photographic evidence of the disease process provided when indicated.

FACTORS INFLUENCING THE OUTCOME OF CONGENITAL INFECTION

GENERAL BIOLOGIC FACTORS

The term "congenital disease" is used here to indicate any manifestation of illness present at birth or shortly thereafter that results from transplacental infection by a microorganism. Table I lists the numerous microorganisms known to cause fetal infection. The specific microorganism is the pri-

TABLE I: MICROORGANISMS KNOWN TO CAUSE FETAL INFECTION AND OCULAR EFFECT[2,3]

CLASSIFICATION	ORGANISM OR DISEASE	CONGENITAL MALFORMATION	CONGENITAL DISEASE	OCULAR MALFORMATION OR DISEASE
VIRUSES	Rubella	+	+	+
	Cytomegalovirus	+	+	+
	Herpes simplex	(+)	+	+
	Varicella zoster	+	+	+
	Mumps	(+)	(+)	-
	Rubeola	-	+	(+)
	Vaccinia	-	+	-
	Smallpox	-	+	+
	Coxsackieviruses B	(+)	+	-
	Echoviruses	-	+	-
	Polioviruses	-	+	-
	Influenza	-	(+)	-
	Human immunodeficiency virus	(+)	+	+
	Hepatitis B	-	-	
	Lymphocytic choriomeningitis virus	-	+	-
	Parvovirus B19	-	+	-
	Epstein-Barr virus	+	+	-
	Western equine encephalitis	-	(+)	-
BACTERIA	*Treponema pallidum*	-	+	+
	Mycobacterium tuberculosis	-	+	-
	Listeria monocytogenes	-	+	+
	Campylobacter fetus	-	+	-
	Salmonella type foca	-	+	-
	Borrelia burgdorferi	-	+	+
PROTOZOA	*Toxoplasma gondii*	-	+	+
	Plasmodium	-	+	+
	Trypanosoma cruzi	-	+	-
FUNGI	*Candida albicans*	-	+	+

Symbols: + = Documented occurrence; (+) = Suggested occurrence (not documented); - = No known occurrence.

mary cause of the fetal infection; however, infection may occur without disease, particularly in reference to the fetal response to microbial invasion.

"Infection" denotes colonization, multiplication, and completion of the pathogenetic process of the organism in the host, including induction of immune response but without producing recognizable pathologic or clinical manifestations.[29] An inadequate challenge dose, an unsuitable portal of entry, or specific host immunity may explain failure of infection to occur. Whether infection causes disease and to what degree, are dependent on the properties of the agent (pathogenicity and virulence) and partly by host defense mechanisms. Many contributing factors influence whether infection will actually occur and whether disease will result.

"Disease" is present when pathologic and clinical changes occur secondary to infection, however, the host system, when exposed to infective agents, may have a gradient response. The several possible outcomes (Fig 1) have been well stated: "Given exposure, infection may not occur; given infection, disease may not result; given disease, it may range from trivial to the fully developed syndrome characteristic of the agent."[29]

Many infants infected *in utero* are asymptomatic at birth or have no signs of congenital disease in early neonatal life. This may be due to fetal infection by a limited inoculum of organisms or with a strain of low virulence or minimal potential for teratogenicity. In contrast, infants exposed to major infection early in gestation may have signs of widely disseminated infection during the neonatal period, reflecting microbial invasion, proliferation, and tissue damage rather than defects in organogenesis. These pathologic processes may have been in progress for weeks or months during gestation but still be self-limited and resolve as defense mechanisms control the spread of the infection and tissue destruction. Both *in utero* infection and infection acquired during the birth process may lead to late-onset disease, inapparent at birth but showing signs months or years later. This is well demonstrated by the recurring chorioretinitis of *T gondii*, delayed hearing deficits of rubella, and the immunologic defects of the human immunodeficiency virus (HIV).[2]

ROUTES OF INFECTION

Infection of the Maternal System. Although pregnant women are regularly exposed to great numbers of microorganisms, only a few ever reach the developing fetus, cause fetal infection, or congenital malformations. Viral infections in the fetus and newborn, however, are not rare and may be present in as many as 6% to 8% of all live births, approximately 3 times the frequency of systemic bacterial disease.[3] Maternal host defense mechanisms are generally very effective in eliminating microbial invaders in the respiratory and gastrointestinal tracts, and the placenta also appears to be

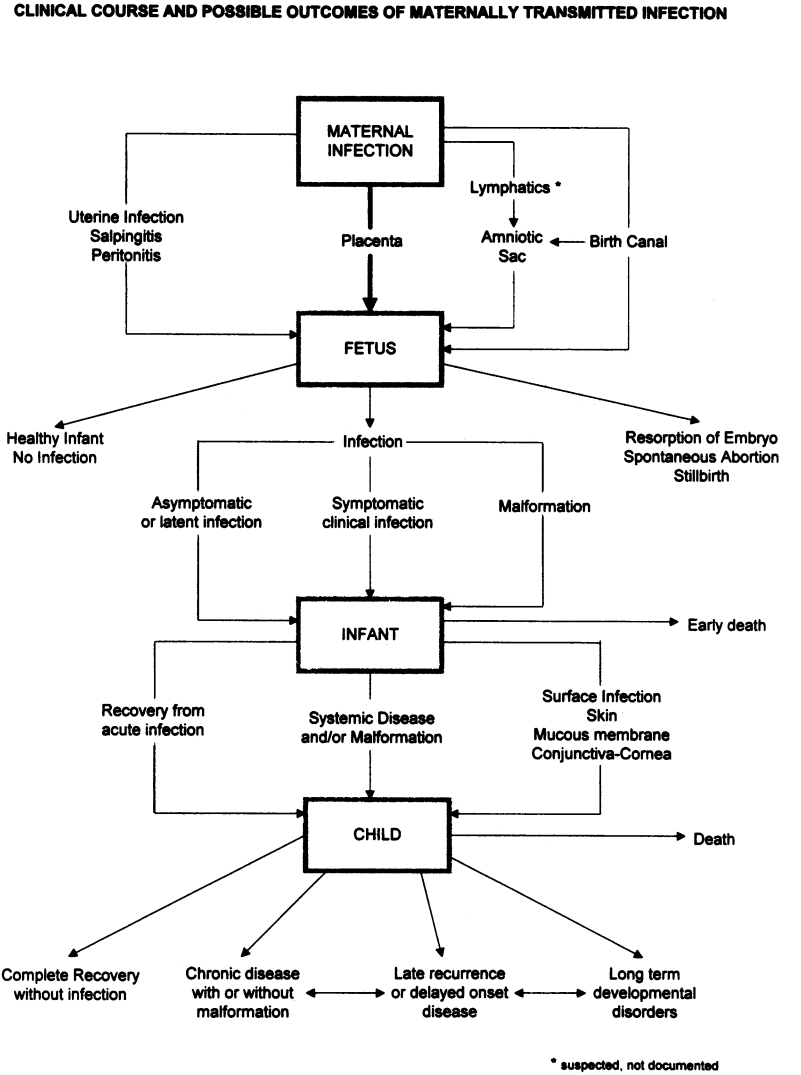


FIGURE 1
Clinical course and possible outcomes of maternally transmitted infection.

an effective protective barrier for the fetus. Consideration of the several routes by which microorganisms are transmitted from the external environment to the maternal and fetal systems to cause defects or infection of the fetal eye is complex (Fig 2). The 2 most common routes by which microorganisms enter the maternal system are through the respiratory and gastrointestinal tracts. Nasal inspiration or oral ingestion of infected

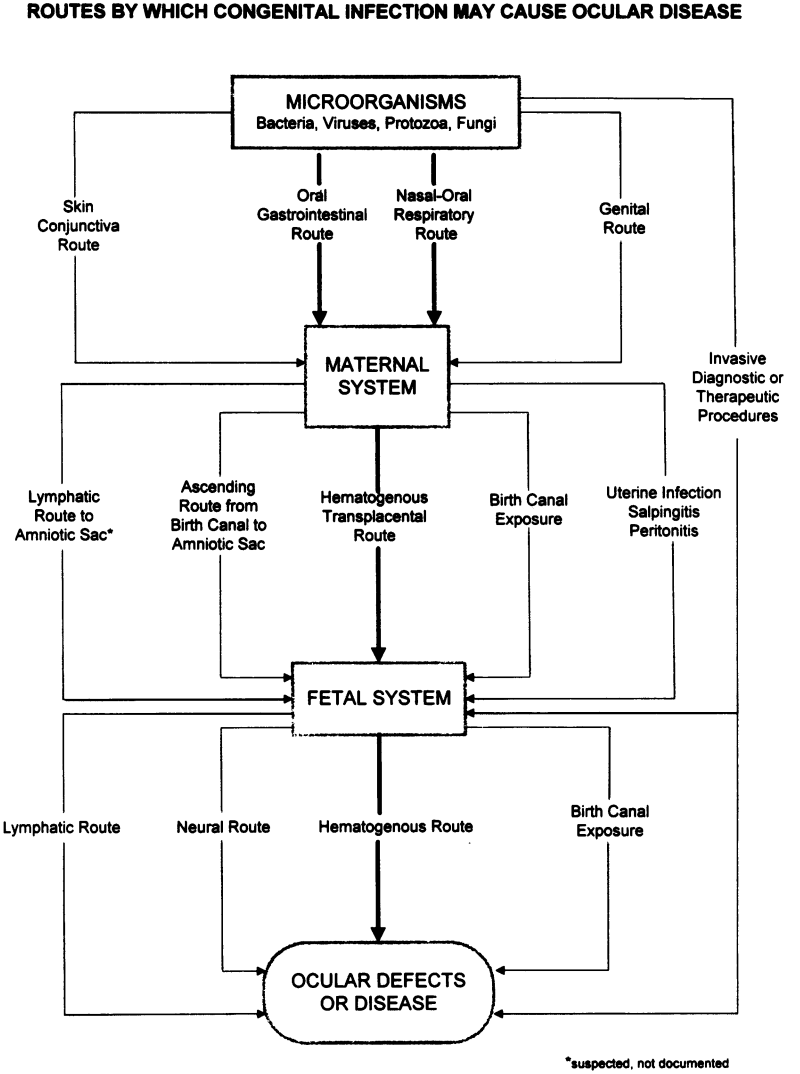


FIGURE 2
Routes by which congenital infection may cause ocular disease.

fomite particles are common occurrences with bacterial and viral organisms, particularly rubella, HSV-1, and varicella. The gastrointestinal system is the most important route of infection for *T. gondii*, which occurs by the ingestion of infected meat or contact with domestic housecats and associated fecal contamination.[32,43] The mucous membranes of the genital

tract are both a source of active infection and a reservoir for several sexually transmitted diseases. Organisms commonly found to infect these tissues and to harbor in them as a chronic source of infection include HIV, herpes simplex virus type 2 (HSV-2), chlamydia, cytomegalovirus (CMV), and *Treponema pallidum*. The least common routes of infection are the skin surface and mucous membrane of the conjunctiva. The tick-borne Lyme borreliosis and mosquito vector of malaria have both been implicated in the causation of fetal infection, and laboratory contamination of the conjunctiva is suspected as a source of acquired toxoplasmosis.[25]

Infection of the Fetal System. The hematogenous route with transplacental transmission is the most common source of fetal infection (Figs 1 and 2). Most microorganisms will pass through the placental barrier, and in instances of massive placental infection, intense focal necrosis, or vascular infarction, even larger organisms will gain entry into the fetal circulation. Another well-described route of contamination of the fetal environment is the ascending route of microorganisms from the maternal cervix or vaginal canal causing subsequent infection of the fetal membranes and amniotic fluid (amnionitis).[2] Such ascending infection may be more likely to occur following premature rupture of the membranes or a prolonged course of labor. It is also known, however, that microorganisms can invade the intact amniotic sac, and it is suspected that small localized areas of pressure necrosis may occur at the cervical os, possibly creating minute channels for organism entry.[29] Transmission of organisms from lymphatic channels through the fetal membranes has been suggested but not documented.[28,30]

An additional but uncommon source of fetal infection has been demonstrated through contamination from localized infection of adjacent structures. Abscesses of the myometrium, endometritis, peritonitis, and descending salpingitis may rarely be additional routes of microorganism transmission to the developing fetus.[2]

Contemporary methods of prenatal diagnosis and fetal therapeutic measures are also uncommon but documented sources of fetal infection. These may include diagnostic amniocentesis, fetal blood sampling, and the insertion of scalp clips for echocardiographic monitoring. Fetal transfusion has been reported to cause overwhelming fetal infection.[2]

Infections of the Eye. The final routes of microbial transmission are those coursing within the fetal system to the target or shock organ, the eye itself (Fig 2 and Table II). The most direct and prominent route continues to be via the bloodstream to the developing eye. The lymphatic system may play a minor role in the transmission of infection.[44] In the absence of cell-mediated or humoral immune defenses until approximately the 20th week of gestation, microbial organsisms pass virtually unchallenged through the capillary network to every part of the eye. Certain

TABLE II: ROUTES OF INFECTION OF MICROORGANISMS KNOWN TO CAUSE OCULAR MALFORMATION OR DISEASE*

ORGANISM OR DISEASE	HEMATOGENOUS TRANSPLACENTAL	ASCENDING INFECTION WITH AMNIONITIS	BIRTH CANAL EXPOSURE	INVASIVE DIAGNOSTIC OR THERAPEUTIC PROCEDURES
VIRUSES				
Rubella	+	-	-	-
Cytomegalovirus	+	+	+	(+)
Herpes simplex type 1	+	+	+	+
Herpes simplex type 2	+	+	+	+
Varicella zoster	+	-	-	-
Human immunodeficiency virus	+	+	+	-
BACTERIA				
Treponema pallidum	+	+	+	-
Mycobacterium tuberculosis	+	-	-	-
Listeria monocytogenes	+	+	+	+
Borrelia burgdorferi	+	-	-	-
PROTOZOA				
Toxoplasma gondii	+	-	-	-
Plasmodium	+	-	-	-
FUNGI				
Candida albicans	+	+	+	+

Symbols: + = Documented occurrence; (+) = Suggested occurrence (not documented); - = No known occurrence documented

*Organisms harbored in the genital tract and commonly known to cause ophthalmia neonatorum are not included.

organisms (herpes simplex virus and varicella-zoster virus [VZV]) may infect the eye directly as a primary infection or harbor in neural ganglia as sites of potential delayed secondary infection.[44] Surface infections of the periorbital skin, conjunctiva, and cornea are common sites of perinatal infections (Table II).

Perinatal Infection. Since the majority of fetal infections are asymptomatic at birth and diagnosis usually occurs in the neonatal period, it is often difficult to differentiate between those conditions in which infection was prenatal in origin, occurred from a late ascending infection, or resulted from intrapartum contact in the birth canal. However, both rubella virus and *T gondii* are generally transmitted to the fetus via the transplacental hematogenous route and such distinctions are less important for these organisms.

ROLE OF IMMUNITY

The mature human host is normally protected against invading microorganisms by an array of protective mechanisms and immunologic responses designed to recognize and eliminate foreignness.[45] The fetus and newborn are particularly vulnerable to infectious agents that take advantage of their relatively immature and inexperienced immune system. The primary transfer of protective antibody from the maternal to the fetal system occurs by way of the passage of IgG immunoglobulin. Immunity to a specific agent which has developed following natural infection or that induced by a vaccine may give permanent lifelong immunity. Immunity acquired passively by injected gamma globulin, however, may be effective for only a short period.

IgG. Maternal IgG accounts for the vast majority of the newborn's immunoglobulin, because almost none is made by the healthy fetus, and IgG is the only maternal immunoglobulin that crosses the placenta. Maternal transport of IgG can be detected as early as 8 weeks gestation, and the newborn IgG level is directly proportional to gestational age (Fig 3).

Although some maternal IgG may be transmitted in the first trimester,

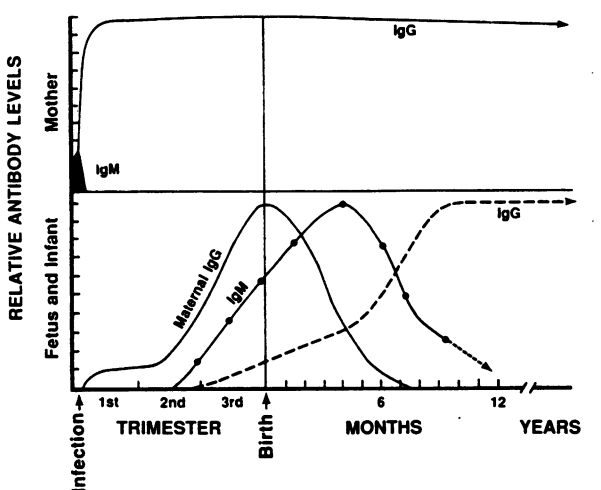


FIGURE 3

Schematic of immune response in the mother, fetus, and infant after maternal and fetal rubella infections in first trimester of pregnancy.

Adapted, with permission, from Alford CA. Immunology of rubella. In: Cooper LZ, Preblud SR, Alford CA. In Remington JS, Klein JO, eds. Infectious disease of the fetus and newborn infant. Philadelphia: Saunders; 1995:282.

the majority of maternal IgG reaches the fetus after 32 weeks gestation and endogenous synthesis does not begin until about 24 weeks gestation. Therefore, the majority of maternal IgG transmission to the fetus is during the last 8 weeks of full-term gestation.[45]

The IgG transferred from the mother to the fetus has been demonstrated to protect the newborn from many infectious agents, including viruses such as varicella, polio, measles, mumps, and rubella, and from bacteria such as tetanus, diphtheria, influenza type B, and group- B streptococcus.[45]

IgM. Exposure to most antigens induces an initial IgM response in the mature immune system, which is followed shortly by an IgG response. Some, but not all, fetuses near term can also make IgM and IgA antibodies to organisms such as rubella and toxoplasma.

The amount of fetal antibody produced is in response to intrauterine antigenic stimulation and is proportional to gestational age.[46] The fetus challenged by infectious organisms in utero responds with antibody production largely of the IgM variety. Since IgM is a heavy substance with a high molecular weight, it does not cross the placental barrier and none is transported from the maternal system. The presence of IgM levels greater than 20 mg/dL in the cord blood or in the infant serum is considered abnormal and suggests the presence of congenital infection.[45,46]

IgA. This is primarily a secretory immunoglobulin that exists primarily on mucosal surfaces, where it is found in all secretions, and is present in a high concentration in breast milk. Since IgA is not absorbed, it persists on the mucous membranes and provides host defenses at the tissue surfaces where it neutralizes viruses, prevents the adherence of bacteria, and reduces the incidence of enteric infections, particularly in breast-fed infants.

IgE. This is produced by plasma cells near gastrointestinal and respiratory mucosal surfaces. Its main function is to trigger immediate hypersensitivity reactions and enhance the release of other immune factors, such as IgG and complement. Although IgE probably plays an important role in protecting against parasitic diseases in the mature host, none is transported to the fetal system from the mother and little is produced in the fetal system before birth.

Cellular Components of the Inflammatory Response. The cellular responses are carried out primarily by phagocytic cells, such as polymorphonuclear leukocytes (PMNs), monocytes, and macrophages, and secondarily by eosinophils and lymphocytes. PMNs are first produced in the liver at about 2 months gestational age. By 5 months of gestation, the bone marrow has become the primary hematopoietic center, and liver production has diminished.[45] The PMN, or neutrophil, is the most abundant phagocyte in the human host and the most important component in the

cellular defense system. Circulating phagocytes, generally adequate by the fifth month of gestation, have 3 primary defense functions: migration to the site of infection, recognition and ingestion of invading microorganisms, and killing and digestion of these organisms.

Immunologic Response to Prenatal Infection. Fetal immune responses vary considerably depending on the specific organisms, the time of gestation, and the competency of the maternal immune system. Diffuse viremia in congenital rubella, for example, incites very minimal immune response, and infection during the first 5 months of gestation may have viral persistence with neonatal infection extending from 6 months to 3 years despite passive antibody acquired from the mother and active antibody synthesis by the infant. After birth the infant may continue to shed virus while making antibodies, and a variety of abnormal antibody responses has been reported in children with CRS, which probably account for an increased frequency of other infections.[45]

The rubella virus appears to incite teratogenic effects and congenital defects during the first 8 weeks of gestation. In later pregnancy, the organism's effect is primarily inflammatory, as evidenced by the hepatitis, iridocyclitis, and meningitis of the congenital rubella syndrome.[45]

MATERNAL FACTORS

Pregnant women are exposed to many microorganisms in their environment. This is particularly true in families where young children often harbor infectious disease. Most such infections in the mother are limited to the respiratory and gastrointestinal tract, posing little risk to the developing fetus. Maternal host defense mechanisms generally respond to prevent infection or to keep them localized and the placenta provides a protective barrier to most microbial agents.

Age appears to be a factor in the frequency of primary viral infections in pregnant women, and the incidence of infection is inversely proportional to maternal age. Because of a relative lack of immunity, young children are particularly susceptible to viral infections and are at a high risk of exposure. The older maternal systems have developed a greater immune resistance and are less susceptible to exposure and infection.[3,29]

Many infectious diseases that eventually will have serious consequences for the fetus are clinically mild and unrecognized in the mother. It has been well documented that only 50% to 60% of women infected with rubella virus will have a recognizable rash, and acquired toxoplasmosis is generally a benign condition in its active stages and frrequently goes undiagnosed in pregnant women.[7]

The key to fetal protection against most microorganisms is the presence of a high level of maternal immunity, such as develops after natural infection or induced by vaccine. Except in rare cases, an absolute immu-

nity is conferred against infection from certain organisms. In the case of rubella virus and *T. gondii*, the fetus is protected by maternal immunity, and infection by these organisms will only occur as a result of primary infection. In the case of CMV and HIV, permanent immunity is not developed and infection may result, either from primary or recurrent infections, and may also occur in multiple pregnancies.[2]

Although maternal host defense mechanisms and the placenta appear to provide a protective barrier for the fetus from most maternal infections, damage to the fetus may occur in the absence of actual fetal infection because of severe systemic illness in the mother or alteration of placental function. Severe nutritional deprivation during pregnancy may affect the size and vitality of the fetus. As nutritional deprivation becomes more severe, first weight, then length, and finally brain mass is affected.[47] Adequacy of the placental circulation becomes a progressively more important factor as pregnancy progresses. Placental ability to provide adequate nutrition may be severely compromised in the presence of placental infection.

FETAL FACTORS

The two most important factors related to fetal susceptibility to infection, particularly in the early weeks of gestation, are the almost total absence of defense mechanisms and the high rate of cell division and rapid growth. It is not until the beginning of the third month of gestation that the fetus begins to develop its nonspecific immune protection to provide a phagocytic response to invading microbial organisms.[46] Although the maternal system produces high levels of IgM in response to acute infection, these are of no benefit to the developing fetus, since IgM molecules will not cross the placental barrier (Fig 3).

To restate the fetal immune status, the fetus remains incompetent to produce IgM until the third trimester, and its major immune protection is provided by the transmission of maternal IgG, which will often not reach effective levels until between the 26th and 32nd week of gestation.[45]

The period of maximum susceptibility to the devastating effects of infectious agents or teratogens extends through the first 20 weeks of gestation with its peak between the 10th and 12th weeks. The most active period of organogenesis is considered to be between days 18 and 40 of gestation for the development of major malformations, excluding genital malformations and cleft palate, which have longer periods of sensitivity.[30,48] Sensitivity of the fetus for induction of mental retardation and microcephaly appears to be greatest at the end of the first and beginning of the second trimester.

It has been well established that the gestational age of the fetus or the time during pregnancy in which the mother is infected is a major factor

influencing both the frequency and severity of fetal tissue damage. Fetal injury from rubella virus infection, for example, will have serious effects on 100% of the infants when infection occurs in the first 11 weeks of gestation, with 8 weeks being the peak of injury. Between the 12th and 20th week, congenital rubella defects are present in 30%, and no defects will generally be present with infection occurring after 20 weeks.[3]

AGENT/ORGANISM FACTORS

Numerous microorganisms have been documented to cause fetal infection and disease. Some have teratogenic potential, and early fetal exposure during the period of organogenesis (particularly during the first 8 weeks of gestation) may result in structural malformations or arrests in organ development. Table I lists all organisms known to have a fetal effect, plus several that are suspected but not documented. Of these various classes of organisms, viruses, bacteria, protozoa, and fungi, several are known to cause significant degrees of fetal morbidity and mortality. Viruses constitute the largest group of organisms known to be transmitted through the maternal systems to the fetus, and of the many families of viruses known to be pathogenic to humans and animals, the greatest number are classified in the herpes family (*Herpesviridae*). These include herpes simplex types 1 and 2, the varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpes virus-6.[49] Although these organisms have a significant cumulative effect as causes of human infection, none have had the major impact on the number and severity of fetal infections as have the rubella virus and the protozoa, *Toxoplasma gondii*.[3]

There are several major factors relating to the microbial agent or microorganism that determines its ability to cause infection and disease. Microbial agents are collectively described as invading, living parasites, and each has properties directly related to its ability to cause disease and to its perpetuation in the host. The organism's ability to infect host tissues and cause disease rely on several specific host-related properties:

- Infectivity: the ability to invade and multiply in a host
- Pathogenicity: the ability to induce disease, which may be affected by the size of the inoculum, or infecting dose
- Virulence: the ability of a microorganism to overcome defense capabilities of the host and cause clinical disease
- Immunogenicity: the ability to induce a specific immunity; for example, rubella virus and *T. gondii* induce solid and long-lasting immunity
- Adherence: many pathogenic microorganisms are thought to be aided in their ability to produce disease by the presence of certain adhesive or adherence properties that allow a pathogen to gain a "foothold" on the mucosal surfaces of the host[50]

All microorganisms also have certain common properties that become

Table III: Nonocular Abnormalities in Congenital Rubella Syndrome

Organ system	May be present from birth Transient defects		Delayed onset or Permanent defects		developmental defects	
general systemic	Hepatosplenomegaly	10-20%	Hepatic fibrosis/deficiency		Endocrinopathies	
	Hepatitis	5-10%	Alteration of immune system		Type 1 diabetes mellitus	20%
	Jaundice		Small stature			
	Thrombocytopenia	5-10%	Delayed/retarded postnatal growth		Thyroid dysfunction hyperthyroidism, hypothyroidism thyroiditis	5%
	Petechiae/purpura		Chronic pneumonitis			
	Intrauterine growth retardation	50-80%				
	Failure to thrive					
	Pneumonitis	5-10%			Growth hormone deficiency	
	Hemolytic anemia				Addison s disease	
	Chronic rash					
	Adenopathy				Hypertension	
	Myositis					
	Diarrhea					
cardiac	Myocarditis		Patent ductus arteriosus	30%	Myocarditis	
	Endocarditis		Pulmonary artery stenosis		Myocardopathy	
	Congestive heart failure		Pulmonary valvular stenosis		Congestive heart failure	
			Coarctation of aorta			
			Atrial/ventricular septal defects			

TABLE III (CONTINUED): NONOCULAR ABNORMALITIES IN CONGENITAL RUBELLA SYNDROME

CENTRAL NERVOUS SYSTEM	Meningitis	10-20%	Chronic encephalitis	Progressive cognitive deficits	
	Encephalitis	10-20%	Mental retardation	10-20%	Late seizure disorders
	Enlarged-bulging anterior fontanelle		Motor deficits		Progressive *severe* panencephalitis
	EEG abnormalities		Microcephaly		
			Cerebral calcification		
			Seizure disorders		
			Autism		
			Behavioral and psychiatric disorders		
			Language disorders		
HEARING DEFICITS*	Peripheral (sensorineural)	80-90%	Continuous and progressive hearing loss		Progressive and late onset hearing loss
	Central		5% — often severe		

*Most common manifestation of congenital rubella.

operative in the causation of infection and that can be considered to occur in 5 major stages:

1. The organism must come into contact with a host, usually at a mucosal surface, and adhere to the site.
2. Proliferation of the organism must occur at the local site, allowing the number of organisms to increase in order to cause disease.
3. A stage of local tissue damage follows.
4. Toxin may be produced and can act locally or systemically.
5. Tissue invasion and dissemination of the organisms to other parts of the body occur.[50]

OBSERVATIONS/RESULTS

RUBELLA

Numerous studies have demonstrated that 70% to 80% of infants born to mothers who had rubella during the first month of gestation will have one or more severe rubella-associated anomalies[6-12] (Table III and Table IV). These include defects of the heart, eyes, hearing organs, or central ner-

TABLE IV: OCULAR DEFECTS IN CONGENITAL RUBELLA SYNDROME

PRENATAL ONSET*	PRENATAL OR POSTNATAL ONSET†	DELAYED ONSET
Iritis	Microphthalmia	Glaucoma
Iridocyclitis	Cataract	Cataract
Corneal clouding	Glaucoma	Optic neuritis
Intraocular pressure elevation	Corneal opacification	Optic atrophy
Virus presence in conjuctiva, aqueous and lens	Retinopathy	Strabismus
	Iris hypoplasia	Nystagmus
	Strabismus	Subretinal neovascularization
	Nystagmus	Keratoconus
	Staphyloma formation‡	Lens absorption
	Phthisus bulbi†	Corneal hydrops
	Visual impairment	

*May be transient.
†Usually permanent.
‡Usually surgical sequelae.

vous system. Whereas hearing deficits, the most common of all rubella-associated defects, may often occur as an isolated defect, with rare exception, ocular anomalies occur in combination with other rubella-related defects.[18,36] Infants who present with cataracts, microphthalmia, or glaucoma, therefore, have generally been subject to widespread viral dissemi-

nation and are often multi-handicapped.

All 34 rubella patients have ocular abnormalities and were confirmed by virus isolation. Patients have been divided into 2 groups according to their entry source and follow-up facilities, either through private ophthalmology offices or the ophthalmology service of a large children's hospital. The former are listed as "private patients" and are recorded in Table V(A). The latter are listed as "clinic patients" and are continued in Table V(B). All of the patients in this series were examined within the first several months of life except for case No. 3 (see Table V), who was referred and first seen at age 8 years after undergoing multiple surgical procedures and also had major adverse sequelae. In addition to their ocular findings, all patients in this series had other major rubella-related defects. The most frequent were congenital heart defects; the second most common were varying degrees of psychomotor retardation; and third were severe hearing deficits (Table III).

Mortality

Of the 16 private patients, 3 are known to be deceased (18%). One death was at age 3 years of unknown cause, 1 at age 13 of a spontaneous pneumothorax, and 1 at age 32 from acute bacterial sepsis. Of the clinic patients, 6 of 18 (33.3%) died early of rubella-related congenital heart defects; 5 infants died by 3 months of age (several during cardiac surgical procedures) and 1 at 16 months. Several clinic patients who were lost to follow-up had multiple cardiac defects and are presumed to be deceased.

Follow-up

Private patients had considerably longer follow-up than clinic patients (Table VI). Twelve of 16 private patients (75%) were observed for more than 5 years, 10 (62%) for more than 10 years, and 6 (37%) for more than 20 years. Of the clinic patients, only 2 of 18 patients (11%) had any continuous follow-up, for 11 and 12 years respectively.

Lost to Follow-up

The multi-handicapped status of the majority of both groups of congenital rubella patients contributed significantly to their families' inability to maintain continuous care. Of the private patients, 7 of 16 (44%) discontinued their private care without explanation and became lost to follow-up. Of the clinic patients, their status is recorded as either "unknown" after their early hospital inpatient or outpatient care or "deceased." Two handicapped children were observed for 11 and 12 years, and only 1 other was observed for 26 months before these 3 also were lost to follow-up.

Table V: Congenital Rubella Syndrome: Long-term Follow-up of Patients Identified with Ocular Defects in Early Infancy

Table V (A): Patients Followed Through Private Ophthaolmology Offices

Case	Living or dead	Time of f/u	Cataract	Microph-thalmia	Retino-pathy	Glaucoma	Cornea	Nystagmus	Last acuity	Long-term status and complications
1	L	32 yr	OU °	OU	+	+ po	+ po	+	enucleation 20/60	Severe glaucoma, corneal-scleral staphyloma, enucleation, MR
2	D	31 yr	OD °	OD	+	-	-	+	HM 20/30	Deaf, acute sepsis Deceased age 32
3	L	18 yr	OU °	OU	+	+ po	+ po	+	enucleation 20/200	Severe glaucoma, corneal ectasia, enucleation, deaf, LTF
4	L	2 yr	OU °	OU	+	+ po	-	+	NLP HM	Severe glaucoma, staphyloma, phthisis bulbi, deaf, MR
5	L	33 yr	OU °	OU	+	+ po	+ po	-	20/200 20/400	Aphakic bullous keratopathy, Keratoplasty × 2
6	L	33 yr	OU °	OU	-	+ po	-	+	FC 6″ FC 6′	Diabetes mellitus, glaucoma Multiple glaucoma procedures
7	L	32 yr	-	enlarged corneas	+	+ Diagnosed at age 1 yr	Haab's stria	_	20/100 20/40	Goniotomy × 2 - OU Trabeculectomy
8	L	15 yr	OU °	OU	+	-	-	+	NR	Chaotic nystagmus, LTF
9	L	5 yr	OU °	OU	+	-	-	+	NR	LTF
10	L	6 yr	OD °	OD	+	-	-	+	eccentric good	Atrophic iris CHD surgery, LTF
11	L	5 yr	OS °	OS	-	-	-	-	NR	CHD surgery, LTF
12	D	13 yr	OU °	OU	-	-	-	+	NR	Pneumothorax Deceased age 13
13	D	3 yr	OU °	OU	+	-	-	-	NR	Deceased age 3
14	L	20 yr	OU °	OU	+	+ po	-	+	NLP <20/400	Severe glaucoma, corneal scleralec-tasia, MR Multiple procedures, LTF
15	L	1 yr	OU °	OU	+	-	-	-	NR	CHD, LTF
16	L	6 yr	OD °	OD	-	-	-	-	10/200 20/20	CHD, deaf, MR LTF

Table V (B): Patients Diagnosed and Treated in Hospital Clinic Facilities

Case	Living or dead	Time of f/u	Cataract	Microph-thalmia	Retino-pathy	Glaucoma	Cornea	Nystagmus	Last acuity	Long-term status and complications
17	D	2 wk	OU	OU	-	-	-	-	-	Microcephaly, CHD Deceased age 2 wk
18	D	2 mo	-	OU	+	transient OU	hazy OU	-		CHD; Deceased age 2 mo
19	U	12 mos	OU *		+	-	corneal edema po	+	HM	Microcephaly; CHD, LTF
20	D	1 mo	OS	OS	-	-	-	-		Microcephaly, CHD Deceased age 1 mo
21	U	13 mo	OU *	OU	-	-	-	+	HM	Deaf, LTF
22	L	11 yr	OU *	OU	-	-	-	+	20/200 20/200	LTF
23	D	1 mo	OD	OD	-	-	-	-		CHD, Hepatitis; Deceased age 1 mo
24	U	2 yr	OU *	OU	-	-	-	-		PMR, LTF
25	D	16 mo	-	OU	-	transient OD	opaque, ectasia OD	-		Lamellar keratoplasty, CHD Deceased
26	U	18 mo	OD *	OD	+	transient OS	-	-		CHD, MR, LTF
27	U	26 mo	OS *	OS	-	-	-	+		Microcephaly, PMR, LTF
28	L	12 yr	OU *	OU	+	-	-	+	"poor"	PMR, LTF
29	U	8 mo	OU	NR	-	-	-	-		PMR, LTF
30	U	3 mo	OU	OU	-	-	-	-		CHD, LTF
31	U	5 mo	-	OU	+	-	half of cornea opaque OD	-		Retinal hemorrhage, chorioretinal scar, deaf, LTF
32	U	3 mo	OU*	OU	-	-	-	-		Marked iris hypoplasia, LTF
33	U	5 mo	OU	OU	-	-	-	+	LP	CHD, deaf, LTF
34	D	3 mo	-		-	transient OU	hazy	+		CHD; Deceased

CHD = congenital heart defect; D = deceased; FC = finger count; F/U = follow-up; HM = handmotion; L = living; LP = light perception; LTF = lost to follow-up; MR = mental retardation; NLP = no light perception; NR = not recorded; OD = right eye; OS = left eye; OU = both eyes; PMR = psychomotor retardation; po = postoperative sequelae; U = unknown; symbols: + = positive; - = negative.

*Early cataract surgery (manual aspiration procedure).

TABLE VI: DURATION OF FOLLOW-UP OF CONGENITAL RUBELLA PATIENTS

TIME	"PRIVATE" PATIENTS	"CLINIC" PATIENTS	TOTAL
0 - 12 mo	1	11	12
1 - 5 yr	3	5	8
6 - 10 yr	2	0	2
11 - 20 yr	4	2	6
21 - 33 yr	6	0	6
TOTAL	16	18	34

Ocular Defects

The infant in Fig 4 (case 17) is representative of congenital rubella syndrome with low birth weight, bilateral cataracts, and multisystem defects.

Cataract. Of the 34 study patients, 29 (85%) had cataracts at birth or at the time of first examination. Twenty-one were bilateral (72.5%), and 8 were unilateral (27.5%). The incidence of cataracts was slightly higher in the private group (15 of 16 patients, or 94%) than in the clinic group (14

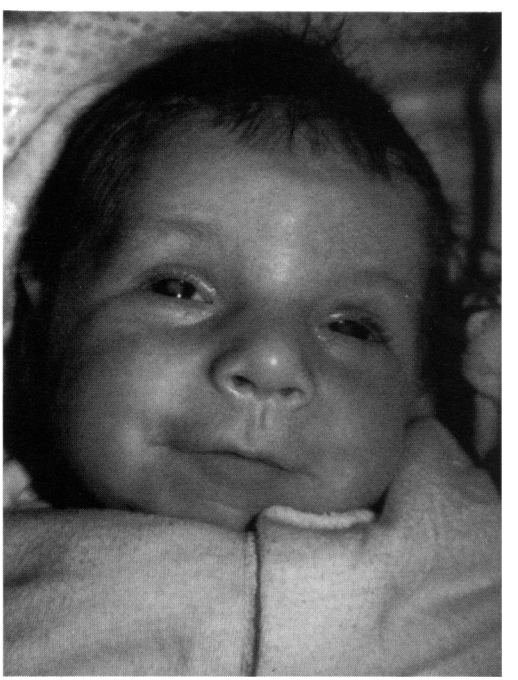


FIGURE 4

Case 17. Full-term newborn infant with culture-proven congenital rubella syndrome. Birth weight was 4 lb 4 oz. Bilateral cataracts, microphthalmia, microcephaly, and hepatosplenomegaly were present. Infant died at age 2 weeks from congenital heart defect.

of 18, or 78%).

Microphthalmia. Excluding 1 case for whom the eye size was not recorded, all cataractous eyes in this series were microphthalmic, except in 1 infant who had bilateral cataracts with both eyes of normal size (case 19). All eyes that were microphthalmic also were found to have cataracts, with the exception of 2 cases. In 1 individual, half of the cornea of 1 eye was opaque (case 31), and in another (case 25), 1 cornea was completely opaque and ectatic and the other eye had a transient corneal haze and intraocular pressure elevation (Fig 5A-C.)

Glaucoma. Only 1 patient in this series of 34 developed an infantile-type glaucoma with enlarged cloudy corneas, elevated intraocular pressure, and Haab's stria (breaks in Descemet's membrane). This diagnosis was confirmed at age 1 year, although ophthalmologic examination 6 months previously had noted only a slight difference in eye size. This individual has had multiple operations, including 2 goniotomy procedures on each eye and a trabeculectomy. The current status is "medically controlled intraocular pressure" after 32 years of follow-up (case 7). Six other cases of severe glaucoma have occurred in aphakic patients. Two eyes developed intractable glaucoma following multiple surgical procedures and subsequently developed corneal, scleral, and corneoscleral staphylomata that resulted in enucleation. In 4 of these 6 patients the glaucoma was bilateral. All were microphthalmic eyes, which initially had cataract aspiration procedures within the first year of life. Each of these eyes was reoperated with at least one, and usually several, capsulotomy or capsulectomy procedures for secondary cataract membrane formation. Onset of glaucoma was usually delayed and not diagnosed until after 6 to 8 years, although glaucomatous changes may have occurred earlier. Examination of these rubella-affected children, who were usually deaf and retarded, was often quite difficult.

Four patients in the clinic group initially presented with a hazy or edematous appearance to the cornea, which was generally associated with increased intraocular pressure. In each case, the altered corneal transparency cleared and intraocular pressure normalized over a short period. Fig 5A is representative of these eyes.

Cornea. Three private patients (cases 1, 3, and 5) had severe corneal changes related to their intraocular pressure elevation and corneal degeneration. Case 5 developed an aphakic bullous keratopathy requiring penetrating keratoplasty, which, following rejection, was repeated. The other 2 abnormal staphylomatous and ectatic corneas were in eyes that were eventually enucleated. Two patients had grossly abnormal corneal development from birth. In case 25 (Fig 5A) the right microphthalmic eye has a hazy cornea and increased intraocular pressure and the left eye an opaque cornea with a large central ectasia. The latter increased in forward

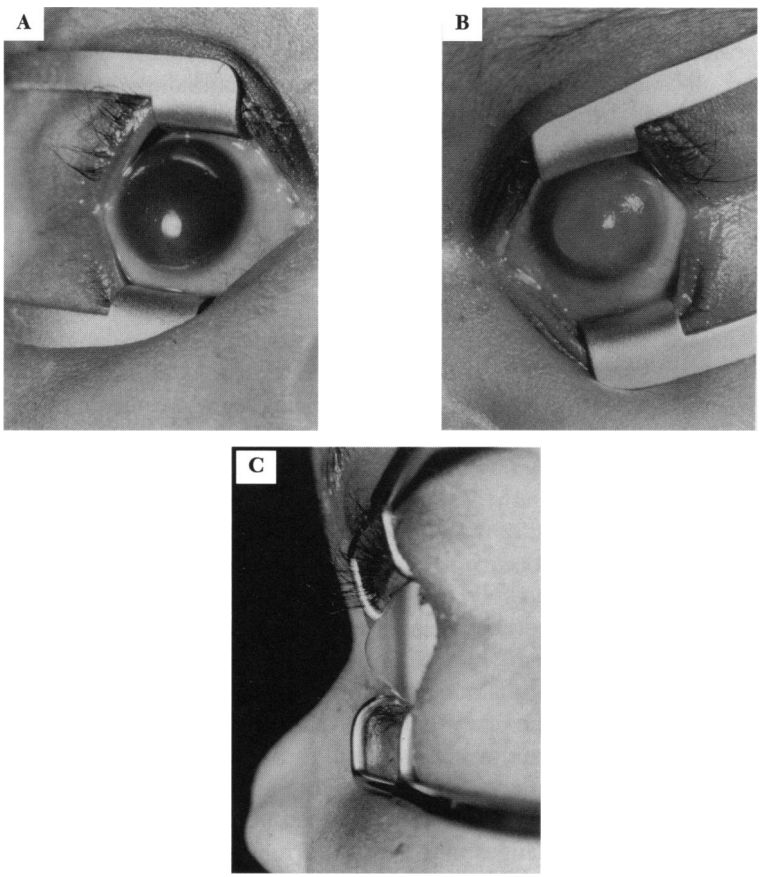


FIGURE 5A*

Infant with culture-proven congenital rubella syndrome (case 25) with slight microphthalmic right eye. Transient corneal haze and early intraocular pressure elevation resolved spontaneously. (AFIP Neg. 65-5801-2)

FIGURE 5B*

Abnormal opaque cornea of left eye (case 25) with large central ectasia for which emergency lamellar keratoplasty was performed because of fear that rupture of ectatic cornea was imminent. (AFIP Neg. 67-5801-3)

FIGURE 5C*

Lateral view of left eye (case 25) with ectatic opaque cornea. (AFIP Neg. 67-5801-5)

* Several previously published photographs and photomicrographs are reproduced through the courtesy of Lorenz E. Zimmerman MD and with permission of the American Journal of Ophthalmology and the Ophthalmic Publishing Company. The histopathologic material of Figs 5A-C, 24A and B, and 26-29 were prepared by Dr Zimmerman and the clinical photos were originally provided by this author in: Histopathologic basis for ocular manifestation of congenital rubella syndrome: The Eighth William Hamlin Wilder Memorial Lecture. *Am J Ophthal.* 1968;65:837-862.

displacement and was imminent to perforation, and a supportive lamellar keratoplasty was performed (Figs 5B and 5C). The isolation of rubella virus provided an unexpected diagnosis for this infant with a grossly abnormal cornea. Case 31 presented with a white and densely opaque plaque involving one half of one cornea, retinal hemorrhages, a chorioretinal scar, and significant hearing impairment.

Retinopathy. Variations in the pigment distribution of the retina were seen in several noncataractous eyes and in the eyes of several individuals after cataract surgery had been performed and the posterior segment visualized. Notations were made as to the presence or absence of characteristic retinal pigmentation; however, unilaterality or bilaterality was not always recorded, and retinal examinations were often difficult and unsatisfactory. Several studies have reported neovascularization in long-term follow-up of rubella retinopathy,[51,52] but none was observed in any patient in this study.

Nystagmus. Nystagmus was present in about 50% of infants and was always more prominent when cataracts were bilateral and surgery was delayed.

Vision. Accurate measurement of visual acuity was usually difficult because of the numerous ocular defects and the nature and severity of retardation and hearing deficits. Often, only estimates of vision were possible.

TOXOPLASMOSIS

Twenty-one patients with a diagnosis of toxoplasmosis based on accepted clinical and serologic criteria have been examined and observed over many years. The longest patient follow-up was 34 years, with 7 individuals observed for 20 years or more and 13 for at least 10 years. Records of several patients observed by other ophthalmologists have been available for review.

Time of Initial Evaluation

Of the 21 patients in the study group, 7 presented for ophthalmologic examination before age 1, 13 before age 4, and all 21 by age 8 (Table VII). The earliest examination (case 1, Table VIII) was performed in the new-

TABLE VII: AGE OF INITIAL OPHTHALMOLOGIC EXAMINATION OF PATIENTS WITH CONGENITAL TOXOPLASMOSIS RANGE: BIRTH - 8 YEARS

AGE-GROUP	NO.	SPECIFIC AGES
Birth - 12 mo	7	Birth, 3, 3, 5, 8, 8, 11 mo
1 - 3 yr	6	1, 2, 2, 2, 2, 3 yr
4 - 8 yr	8	4, 4, 4, 4, 4, 5, 6, 8 yr

TABLE VIII: FOUR GROUPS OF PATIENTS ILLUSTRATING THE BROAD SPECTRUM OF POSSIBLE OUTCOMES FOLLOWING CONGENITAL TOXOPLASMOSIS INFECTION (GROUPS BASED ON SEVERITY OF DISEASE AND DEGREE OF DISABILITY)

CASE	AGE AT DIAGNOSIS	REASON FOR INITIAL EXAM	NEURODEVELOPMENTAL STATUS		
			SEIZURE ONSET	NEUROLOGIC SIGNS OR SYMPTOMS	COGNITIVE/ EDUCATIONAL STATUS
GROUP I: SEVERE OCULOCEREBRAL DEFECTS; BLINDNESS; PSYCHOMOTOR RETARDATION					
1	prenatal	Hydrocephalus Cerebral calcification	4 yr	Hydrocephalus Cerebral calcification Lower extremity paresis	Severe psychomotor retardation Minimal speech Hemiparesis
2	3 mo	Strabismus	8 yr	Microcephaly Cerebral calcification	Moderate mental retardation
GROUP II: BILATERAL CENTRAL RETINOCHOROIDITIS; MODERATE NEUROLOGIC SEQUELAE					
3	14 mo	Nystagmus	16 yr	Cerebral calcification Nystagmus Headaches	Master's degree in Education
4	5 mo	Strabismus Nystagmus	None	Cerebral calcification Nystagmus	Mild learning disability High school senior Headaches
GROUP III: UNILATERAL CENTRAL RETINOCHOROIDITIS; MINIMAL NEUROLOGIC SEQUELAE					
5	4 yr	Failed vision screening	None	None	Mild learning disability 4th grade
6	8 mo	Strabismus	None	None	National Merit Scholar Law school graduate
GROUP IV: MINIMAL VISUAL OR NEUROLOGIC SEQUELAE					
7	4 yr	Strabismus	None	None	College degree Teacher
8	4½ yr	Strabismus	None	None	Age 12 Good student

CF = complement fixation; FA = fluorescent antibody; FC = finger Count; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; HA = hemagglutination; NLP = no light perception; PVD = posterior vitreous detachment; RD = retinal detachment

*The highest hemagglutination titer ever recorded at Center for Disease Control at time of testing (1967).

TABLE VIII (CONTINUED): FOUR GROUPS OF PATIENTS ILLUSTRATING THE BROAD SPECTRUM OF POSSIBLE OUTCOMES FOLLOWING CONGENITAL TOXOPLASMOSIS INFECTION

INITIAL SEROLOGY	OCULAR STATUS				YEARS OF FOLLOW-UP	TREATMENT AND CLINICAL COURSE
	RETINO-CHOROIDITIS LOCATION	EVIDENCE OF RECURRENCE	VISION	OCULAR FINDINGS		
1:8,000 Dye	Extensive macular	Multiple	NLP	Microphthalmia	10	Daraprim and sulfa for 1 yr
	Peripheral		NLP	Chronic vitreitis		Retinal detachment surgeries
				Traction retinal detachments		
				Phthisis bulbi		
1:4,096 HA	Extensive macular	Multiple	Enucleation	Esotropia	26	Daraprim and sulfa for 6 wk
	Peripheral		NLP	Microphthalmia		Retinal detachment surgeries
				Chronic vitreitis		Enucleation
				Traction retinal detachments		
				Phthisis bulbi		
1:40,960 HA*	Large macular	Multiple	20/200	Esotropia	30	Laser retinopexy
1:256 CF	Peripheral		FC	Nystagmus		Strabismus surgery
				High myopia		Contact lenses
				Retinal detachment		Thyroid disorder
				Optic atrophy		
1.68 ELISA	Paramacular	Several	20/80	High myopia	15	Daraprim and sulfa, 1 mo
	Peripheral		20/200	Nystagmus		Corrective lenses
				Exotropia 90$_{\Delta}$		Strabismus surgery
				Retinal detachment		Minimal traction RD resolved by PVD
102.86 IgG/EIA	Macular only	None	20/200	Single macular lesion	7	Corrective lenses
0.27 IgM			20/20	Myopia		
1:6,000	Macular	Small	HM	Large, densely pigmented	34	Strabismus surgery
	Peripheral	Peripheral	20/20	macular lesion		Glasses
				Esotropia		
1:256	Macular	Several	20/60	Atypical macular lesion	27	Daraprim and sulfa for 1 mo
	Paramacular		20/20	Vitreal traction band		Sub-Tenon's steroid injection
	Peripheral			Accommodative esotropia		
1:16 FA	Single discrete	None	20/20	Hypermetropia	7	Corrective lenses
	peripheral lesion		20/20	Accommodative esotropia		

born nursery following a prenatal diagnosis of hydrocephalus and cerebral calcification. Three other patients diagnosed before age 6 months have central vision loss related to macular retinochoroidal lesions and mild to moderate CNS sequelae, two with microcephaly.

Patients first examined between the ages of 6 months and 12 months (one 14-month included) have varying degrees of CNS and visual involvement. Two have macular lesions with no central vision in 1 eye, and the third has bilateral macular lesions but visual acuity recorded as 20/60 in each eye. One of this group has moderate to severe mental retardation, one has a minimal learning disability, and one is a National Merit Scholar who completed law school (case 6, Table VIII).

Presenting Signs or Symptoms or Reason for Initial Ophthalmologic Examination

The most common reason for these children to present for ophthalmologic examination was strabismus. Ten (48%) of the 21 children presented because of parents' observations of an ocular deviation. Their ages ranged from 3 months to 4 years. Esotropia was present in 8 children and exotropia in 2. Two additional patients presented with nystagmus and associated strabismus, and a single patient presented with a head tilt. The entire group constitutes a total of 13 of 21 or (62%) of who were first examined for reasons related to an ocular motility disturbance. Additional reasons for presentation included 4 children who failed vision screening tests either at the pediatrician's office or at preschool screening 4 of 21 (19%), and 2 who presented for routine ophthalmologic examination 2 of 21 (9.5%). Two other infants were examined as part of general evaluation for early CNS abnormalities (9.5%). Both of these infants were initially examined in the neonatal period before 3 months of age, 1 with hydrocephaly and 1 with microcephaly (Table IX).

Spectrum of Outcomes in Congenital Toxoplasmosis

This study confirms the observations of many investigators that congenital toxoplasmosis may have a broad spectrum of outcomes. Infection and disease primarily affect 2 major organs that are particularly susceptible to *T. gondii* in humans—the brain and the eye. Table VIII illustrates this varied severity of disease and degree of disability with two representative patients in each of four groups.

Group I of Table VIII consists of 2 patients severely affected by toxoplasma infection. The initial diagnosis of congenital toxoplasmosis for case 1 was suspected following a standard ultrasound study in the fifth month of gestation. Early hydrocephalus and cerebral calcification were noted, and this child has had continuing evidence of severe brain damage since birth. Central nervous system injury has included hydro-

TABLE IX: PRESENTING SIGNS OR SYMPTOMS OF PATIENTS WITH CONGENITAL TOXOPLASMOSIS: REASON FOR INITIAL OPHTHALMOLOGIC EXAMINATION

CONDITION	NO.	REMARKS
Strabismus	10	Ages: 3 mo - 4 yr Esotropia - 8 Exotropia - 2
Nystagmus/strabismus	2	Ages:- 5 mo, 14 mo Esotropia - 2
Early central nervous system abnormality	2	Prenatal hydrocephaly diagnosis Age 3 mo - microcephaly
Failed vision screening	4	Ages: 4 - 8 yr
Routine exam	2	Ages: 4, 6 yr
Other: torticollis	1	Age: 2 yr

cephalus (treated by ventriculoperitoneal shunt with revision), severe psychomotor retardation with hemiparesis, an inability to walk, minimal speech, and seizures since age 4 years. The left eye has been microphthalmic since birth with chronic and recurrent vitreitis and both posterior and anterior uveitis. This eye has had no light perception, and progressive pupillary seclusion, and a prephthisical condition has existed for several years. The right eye has had recurrent retinochoroiditis, chronic and progressive inflammation with vitreitis, traction retinal detachments, and cataract formation. Lensectomy with vitrectomy and membrane peeling has failed to salvage the progressive course of fibrovascular scar formation and 360% retinal detachment. This unremitting course of inflammation and degeneration reflects the most severe ocular sequelae of early intrauterine toxoplasma infection. A 1-year course of pyrimethamine (Daraprim), sulfa, and leucovorin initiated at age 2 months failed to alter this devastating inflammatory process.

Case 2 presented with microcephaly and mental retardation of a lesser degree. The ocular course, however, has been similar, consisting of an initial unilateral microphthalmia with chronic inflammation, including vitreitis. Progressive traction retinal detachments were unresponsive to vitreoretinal surgery of the fellow eye and have resulted in total blindness. Serial photographs (Figs 6-15B) demonstrate the course from initial presentation at age 3 months with bilateral ocular involvement (Figs 6-8) through the period of chronic inflammation and degeneration. The inflammatory process may have provoked chronic irritation or discomfort and stimulated the child's repetitive manipulation of the eye (Fig 9), causing multiple episodes of anterior chamber hemorrhage, which accompanied a gradual phthisical course (Fig 10).

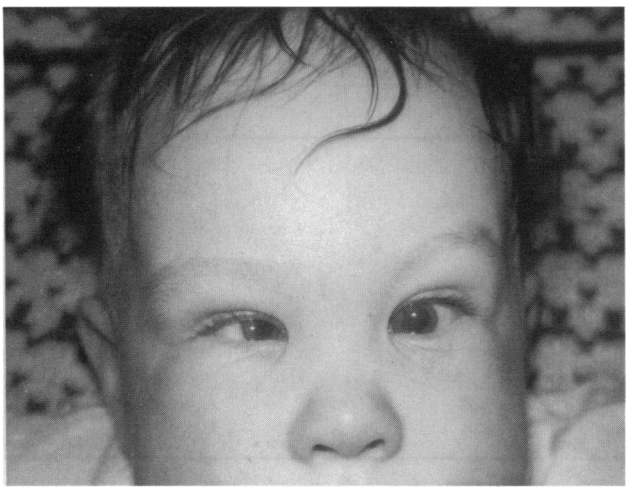


FIGURE 6
Case 2. Three-month-old infant presented with bilateral ocular abnormalities. Right eye shows esotropia and microphthalmia. Pathology also includes multiple posterior synechia, partial persistence of the pupillary membrane, diffuse vitreitis, and suggestion of active focal retinochoroiditis.

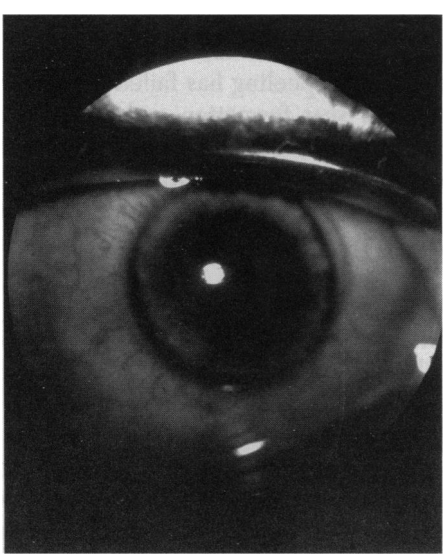


FIGURE 7
Case 2. Right eye showing chronic inflammation, posterior synechia, and persistence of papillary membrane.

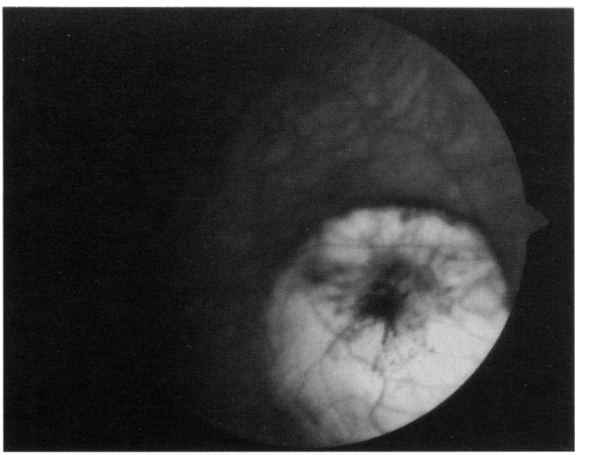


FIGURE 8
Case 2. Retinal photo of left eye with large, inactive macular retinochoroidal lesion.

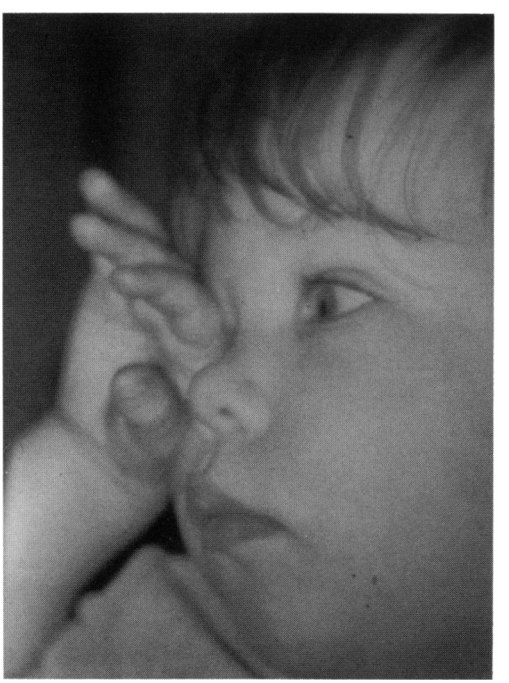


FIGURE 9
Case 2. Chronic inflammation and characteristic manipulation of right eye at age 18 months.

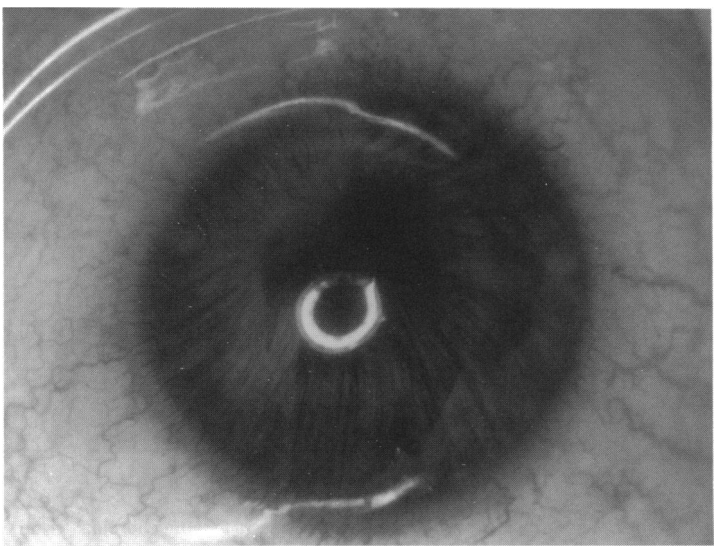


FIGURE 10
Case 2. Age 8, right eye with multiple recurrent anterior chamber hemorrhages, pupillary seclusion, cataract, chronic inflammation, and early phthisis bulbi (pre-enucleation photo).

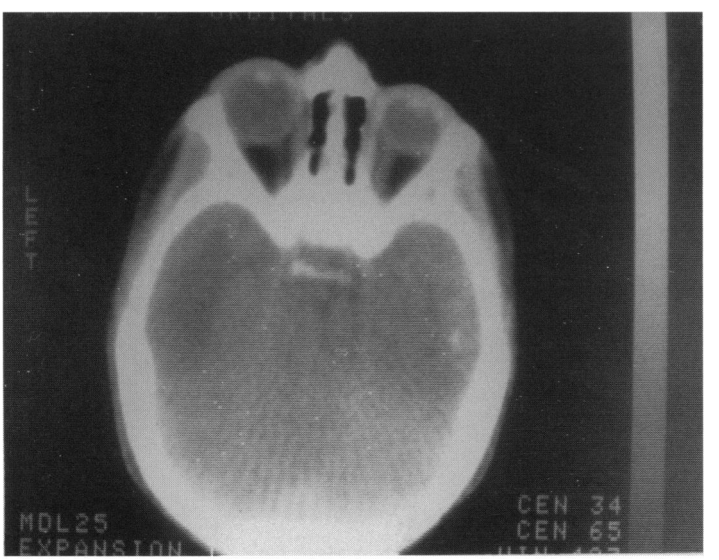


FIGURE 11
Case 2. Early computed tomographic scan showing microphthalmic right eye and parenchymal cerebral calcifications.

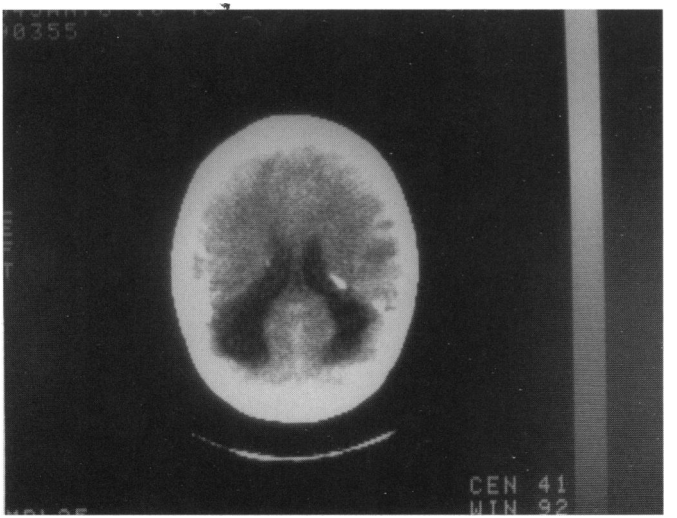


FIGURE 12
Case 2. Computed tomographic scan showing paraventricular calcifications and ventricular enlargement.

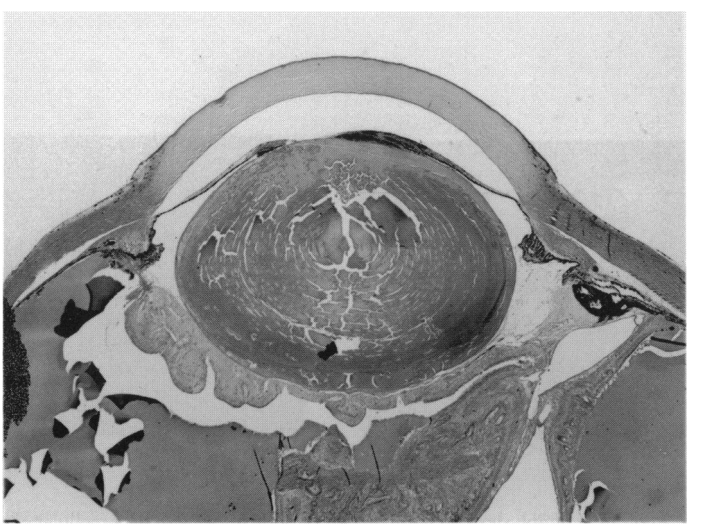


FIGURE 13
Case 2. Photomicrograph showing swollen cataractous lens, pupillary seclusion, detached and degenerated retina adherent to cyclitic membrane, extensive retinal and vitreal neovascularization, and atrophic, rubeotic iris with chronic inflammation (hematoxylin-eosin × 7.5). (AFIP accession No. 1686021)

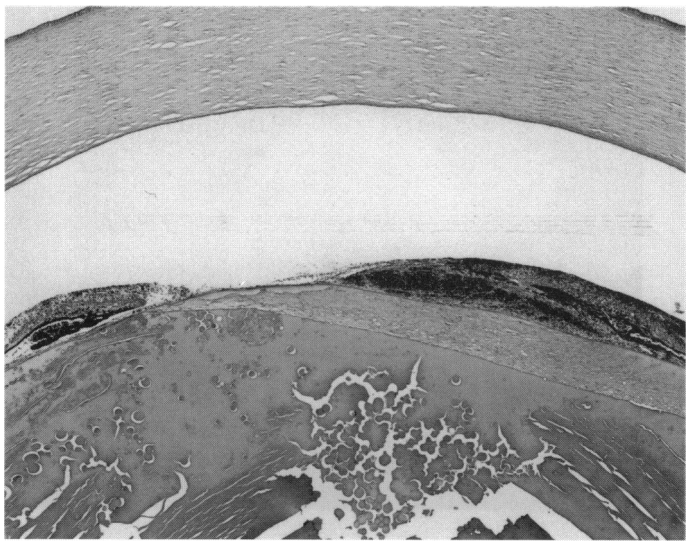


FIGURE 14
Case 2. Higher magnification demonstrates swollen, anteriorly displaced, cataractous lens, vacuolization, and subcapsular fibrous plaque. Pupil is occluded by fibrovascular membrane and posterior synechiae (hematoxylin-eosin × 30). (AFIP accession No. 1686021)

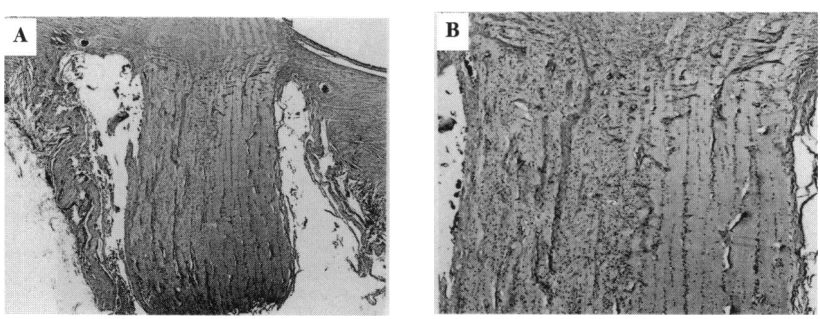


FIGURE 15A
Case 2. Photomicrograph showing hemiatrophy of optic nerve with hypercellular gliotic reaction of left half of nerve. Presumably represents retrograde atrophy related to large macular lesion of toxoplasmic retinochoroiditis in early infancy (hematoxylin-eosin × 30). (AFIP accession No. 1686021)

FIGURE 15B
Case 2. Higher magnification of optic nerve with hemiatrophy (hematoxylin-eosin × 75). (AFIP accession No. 1686021)

CT scans show microphthalmic right eye and cerebral calcification (Figs 11 and 12). Following enucleation at age 8 years, histopathologic slides from 1979 confirm chronic inflammation, pupillary seclusion, cataract formation, and disorganization of the posterior segment structures (Figs 13 and 14). They also demonstrate hemiatrophy of the optic nerve, presumably representing retrograde atrophy from macular lesions (Figs 15A and 15B).

Group II of Table VIII represents a degree of toxoplasmic infection and tissue damage of slightly less severe degree. There continues to be significant ocular damage but less severe neurodevelopmental effect. Cases 3 and 4 presented at a later age with nystagmus and strabismus and have been followed since infancy. Although having large macular lesions with no central vision and a constant nystagmus with broad amplitude (Fig 16), case 3 has proceeded with considerable independence to achieve a Master's Degree in Education and teaches full-time. Case 4 has had only a mild learning disability and 20/80 acuity in the better seeing eye related to macular and paramacular lesion scars. Early retinal examination detected an area of retinal elevation related to a vitreal traction band, which resolved by spontaneous posterior vitreous detachment.

Group III of Table VIII represents those individuals who are asymptomatic in their early months and may later develop strabismus related to poor central vision. If ocular alignment is maintained, these lesions may not be detected for years (case 5, Fig 17). Central nervous system abnormalities may be minimal or nonexistent, and the degree of visual disturbance is dependent on the area and extent of the original retinochoroidal inflammation. Recurrences have been minimal, and there is little effect on the intellectual development (case 6, Fig 18)

Group IV of Table VIII illustrates those individuals who may have focal areas of retinal inflammation and scarring in the absence of any apparent central nervous system involvement. Although case 8 (Fig 19) represents the least possible retinal involvement with a single discrete mid-central lesion, there was positive fluorescent antibody serologic confirmation in both the child and mother. Further complications or sequelae were not observed over a 7-year period.

Case 7 documents the retinal changes of toxoplasmic retinochoroiditis by serial fundus photographs over a 25-year period (Figs 20, A-K).

NEURODEVELOPMENTAL STATUS

Table VIII illustrates the decreasing degree of central nervous system involvement in Groups I through IV. Seizure disorders have occurred at varying periods, and cases 1 and 2 each had visible areas of cerebral calcification on cranial imaging. Case 3, however, had no calcification in the

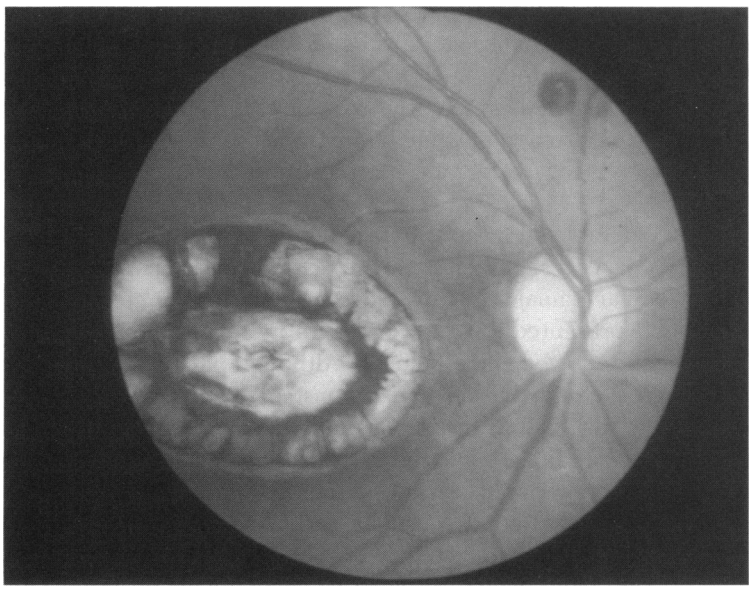


FIGURE 16
Case 3. Large, inactive macular lesion with atrophic center and irregular pigmented border and retrograde temporal optic atrophy. Considered to be the "classic macular lesion" of early gestational congenital toxoplasmosis. (Early texts often mistakenly used the term "macular coloboma.")

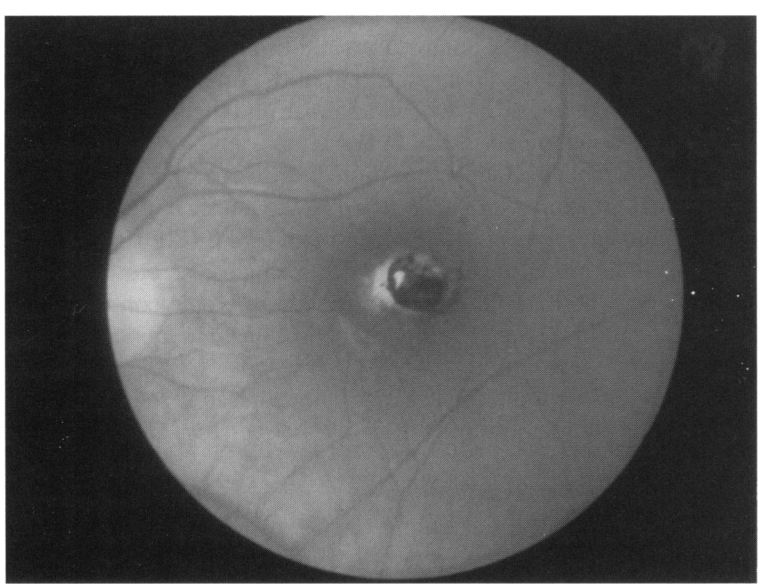


FIGURE 17
Case 5. Small, round, deeply pigmented, solitary, inactive lesion.

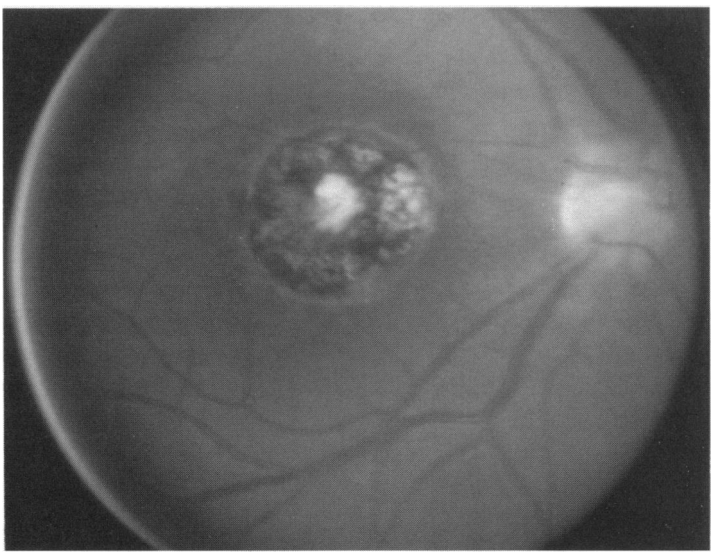


FIGURE 18
Case 6. Circular, circumscribed, inactive retinochoroidal lesion with irregular scattered areas of atrophy and pigment accumulation.

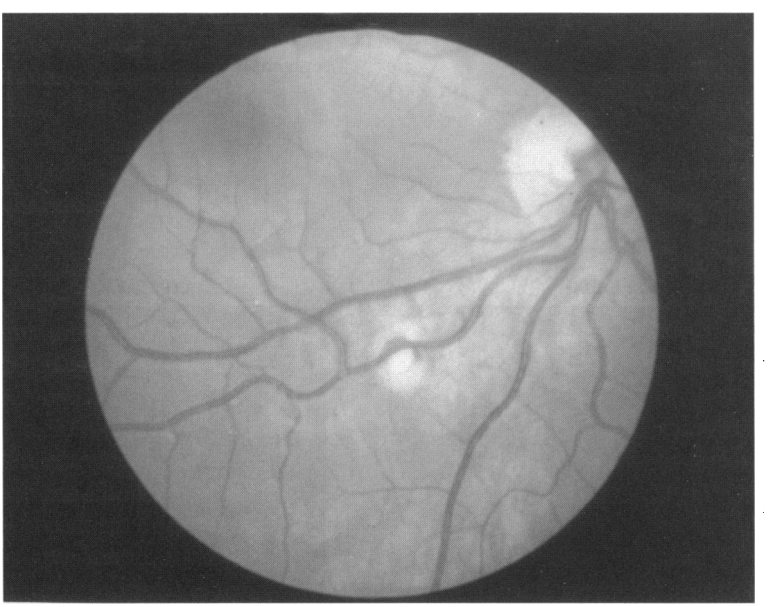


FIGURE 19
Case 8. Single, small, solitary, atrophic lesion with partially pigmented corona. 20/20 vision OU. Completely normal retina otherwise.

FIGURES 20 A-K

Case 7. This series of retinal photographs illustrates the change in clinical appearance of toxoplasmic retinochoroiditis lesions in the same patient's right and left eyes over a 25-year period.

ACUITY 10/200

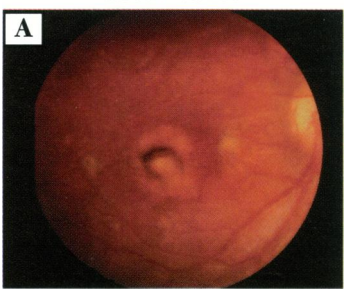


FIGURE 20A

Right eye shows atypical macular lesions with several paramacular satellite lesions.

AGE 7
1972

ACUITY 20/20

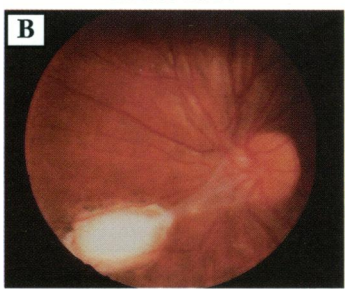


FIGURE 20B

Left eye shows large lesion in inferior nasal quadrant 1 disc diameter from optic nervehead in subacute inflammatory stage with progressive development of vitreal traction band.

ACUITY 5/200

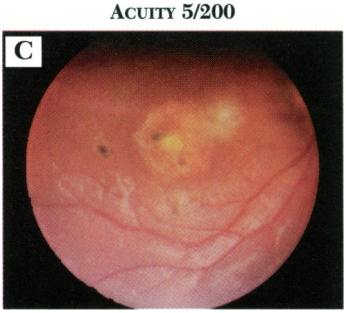


FIGURE 20C

Note active inflammation of paramacular satellite lesion in right eye. Treatment consisted of 6-week course of Daraprim and sulfa.

AGE 8
1973

ACUITY 20/20

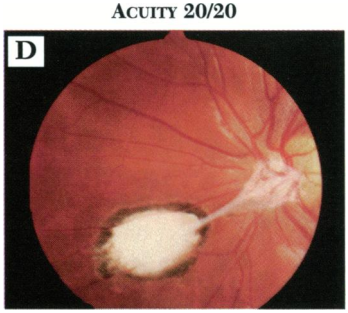


FIGURE 20D

Persistent subacute inflammation of center of large lesion with increasing vitreal traction band in left eye.

ACUITY 20/80

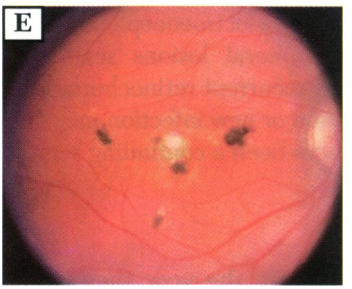


FIGURE 20E
Early sector atrophy of temporal margin of optic nervehead of right eye.

AGE 13
1978

ACUITY 20/20

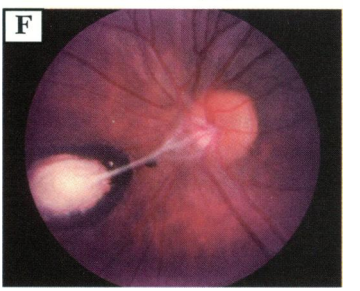


FIGURE 20F
Increasing pigment deposition of inactive lesion and progressive vitreous traction band in left eye.

ACUITY 20/50

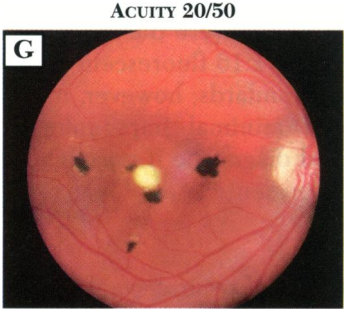


FIGURE 20G
Increasing pigmentation of paramacular satellite lesions and temporal optic atrophy in right eye.

AGE 28
1993

ACUITY 20/20

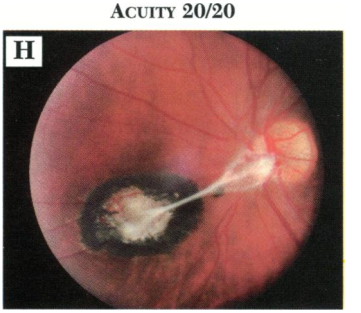


FIGURE 20H
Early neovascularization within a central, inactive lesion in left eye.

ACUITY 20/40-1

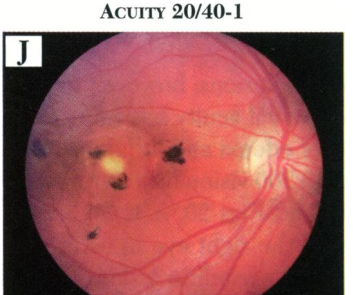


FIGURE 20J
Increasing density and fragmentation of paramacular pigment deposition, early subretinal paramacular neovascularization, and increasing temporal optic nerve atrophy of right eye.

AGE 32
1997

ACUITY 20/20

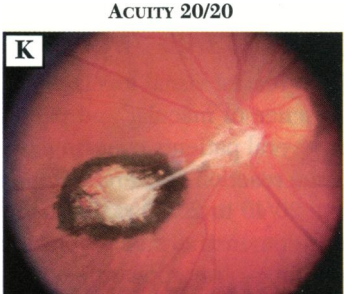


FIGURE 20K
Gradually increasing neovascularization within an old, inactive lesion and dense vitreal band extending from the central lesion to optic nervehead in left eye.

early neonatal period, but at the time of seizure onset at age 16, "calcium deposits in the brain" were noted in CT scans and electroencephalograms showed "brain damage." Several small peripheral lesions scattered through the posterior retina indicated areas of recurrent retinochoroiditis and also suggest that similar areas of reactivation or new infection may be present in the cerebral tissues. Headaches have been a continuing symptom of this patient.

Initial Serology

Specific serologic studies varied, depending on the year they were performed and the facility doing the testing. Case 1, for example, was included in a national toxoplasmosis study that performed a Sabin-Feldman dye test in addition to other confirmatory serologic studies. As noted, the 1:40,960 hemagglutination test recorded on case 3 was the highest that had ever been recorded at that time at the Centers for Disease Control. Other specific tests were the accepted norms at the time of patient examination. The 1:16 fluorescein antibody (FA) titer in case 8 is low by systemic standards; however, minimal ocular infection is known to incite minimal immunologic response and any positive titer is considered diagnostic if a morphologically compatible lesion in the fundus is present.[31]

Evidence of Recurrence

There has been both direct and indirect evidence of recurrence of active inflammation in the area of old retinochoroidal scars (Fig 20C), and new lesions have occurred in what had previously been normal, uninvolved retina. A flare-up of vitreitis has also occurred at times when the visualization of active retinal lesions could not be documented early in the course of infection.

Vision

The greatest visual loss is associated with macular lesions; however, in the presence of macular and paramacular lesions, visual acuity has improved in several patients over time, with resolution of edema and inflammatory tissue reaction. Several lesions with less than 20/200 vision have improved to a 20/40 to 20/60 range (case 7, Table VIII, and Figs 20, A-K). Case 7 also demonstrates an atypical macular lesion of the right eye in its initial and long-term appearance with the activation of a satellite lesion in Fig 20C. Gradual shrinkage of the macular lesions of the right eye led to improvement of vision to 20/60 at the time of Fig 20K, which also shows some gradual fragmentation and decrease of the density of the pigment deposition in the small lesions

Treatment and Clinical Course

Several patients in this series had treatment generally consisting of pyrimethamine with sulfadiazine supplemented with calcium leucovorin. Only one case (case 1, Table VIII), the most severely affected, received therapy over a full 1-year period. Three other patients received the same regimen for periods varying from 4 weeks to 6 weeks (cases 2, 4, and 7). Case 7 also received 2 sub-Tenon's injections of triamcinolone during a period of active inflammation. It is of interest that case 1 had the most severe infection and sequelae, which progressed to phthisis bulbi in 1 eye and total retinal detachment in the second eye despite specific antiprotozoan therapy for 1 year. This clinical course lends support to both clinical and in vitro studies that these drugs may be effective against circulating tachyzoites in the proliferative stage but have little effect on organisms encapsulated in tissue cysts, which have the potential to reactivate at any time.

Associated Ocular Findings

Obvious microphthalmia was present in several patients at the time of birth. These eyes have also exhibited evidence of early severe retinochoroiditis, chronic inflammation, and recurring vitreitis. Anterior uveitis has also been present with pupillary seclusion and cataract formation (case 2 and Figs 7, 13, and 14)

Strabismus and nystagmus are often associated findings with either the loss of central vision or central nervous system impairment or both. Thirteen of the 21 study patients (62%) presented with strabismus or nystagmus as their primary complaint (Table IX).

Retinal Detachment

Four patients (6 eyes) of this study group have had documented retinal detachments to date. Two have occurred in microphthalmic eyes with chronic vitreitis and progressive degeneration, 1 confirmed by pathologic examination and one by ultrasound. The fellow eye in each of these patients has undergone chronic recurrent inflammation and developed progressive vitreal traction bands with extensive detachments, which were not resolved by vitrectomy, membrane peeling, or scleral buckling. Both have progressed to total detachment and blindness (cases 1 and 2). Case 3 with large bilateral macular lesions and multiple small peripheral lesions has had 2 separate areas of traction detachment appearing several years apart, which were successfully treated by laser retinopexy. Case 4, being observed serially by a retinologist, had a minimal area of traction detachment that resolved following spontaneous posterior vitreous detachment.

Case 7 (Figs 20, B,D,F,H,K) provides a vivid visual illustration of the progressive traction of a vitreal band extending from the center of a large,

inactive, retinochoroidal lesion to the surface of the optic nervehead. It is apparent that progressive traction of this degree on an area of less secure retina would have a dire result.

DISCUSSION

RUBELLA

The ocular effects of CRS have been extensively studied through the years following the last major rubella epidemic in the mid 1960s. The majority of patients exhibiting CRS are the long-term survivors from that postepidemic period. Many were seriously affected and compose a segment of the population that has been multi-handicapped, including varying degrees of mental retardation, motor pareses, severe hearing and vision deficits, and a susceptibility to generalized infection. Many have required special education and institutional or custodial care, and except for those individuals with isolated hearing deficits, most are unable to live an independent or productive life.

It is generally recognized that the period during which the fetus is most vulnerable is the first 8 weeks of gestation.[1-4,6,7,12,17,18,30,31] This corresponds to the period of most active organogenesis and most rapid cell division. Among infants whose mothers had rubella during the first month of gestation, 70% had one or more severe rubella-associated anomalies.[7,18] Some studies have indicated even higher rates of defects during this period; however, it is reasonable to conclude that nearly every fetus infected with rubella virus during the early weeks of gestation develops in an abnormal manner.[18] Maternal infection that occurred toward the end of the first trimester or later often resulted in less severe (nonteratogenic) sequelae, but hearing defects have been noted to occur on a continuing basis, through 10 years of life.[53] Hearing deficits of a sensorineural type composed the single greatest disability associated with CRS.

Patients in this study have had a higher than normal mortality rate. The earliest period of rubella-related death occured during late gestation with a high incidence of spontaneous abortion, stillbirth, or subsequent, neonatal death. This fetal and early neonatal mortality occurred primarily in association with early first-trimester maternal infection and its related cardiac malformations and chronic pneumonitis. The mortality rate for affected infants continued to be higher than in the average population through infancy and childhood, particularly among those with persisting cardiac defects.

The broad spectrum of abnormalities observed in the fetus and newborn following transplacentally transmitted rubella infection are listed in Table III. Because of the persistent and long-term effects of intrauterine rubella virus infection, these many abnormalities are best understood

when considered in 3 time periods although there is obvious overlap and continuity. Defects in the first group are considered to be *transient* since they can be present at or before birth. These conditions result from infection or inflammation and are not related to structural malformations. Most will gradually resolve through the early neonatal period. The second group of *permanent* defects may also be present at birth but reflect malformation or tissue damage that will not diminish or disappear with the course of time without intervention or specific therapy. Meningoencephalitis, for example, may gradually become inactive; however, the resulting cerebral damage may only become manifest over months or years. The third group of *delayed-onset or developmental defects* generally appear in childhood or later years and may be progressive in nature.[46,51,52,54-57]

The pathogenesis of these late-appearing defects is not fully understood but may be due to a continuing, subacute, active rubella infection leading to direct viral damage, vascular insufficiency, and possibly triggering autoimmune mechanisms.[17,35,58,59] This group of delayed conditions was first observed in a long-term follow-up study of Australian patients 25 years after the original 1941 epidemic. Various endocrinopathies were identified, the most frequent of which was type 1 diabetes mellitus. This endocrinologic disorder has been recorded in as many as 20% of CRS patients by the age of 35 years, a risk factor of 100 to 200 times that observed for the general population.[54] This apparently can occur in any congenitally infected patient, regardless of the time of maternal exposure.

Thyroid dysfunctions have also been identified as late-appearing defects in a much higher incidence than in the general population. A 2-year-old and a 3-year-old patient with CRS have each been noted to have thyrotoxicosis, and thyroiditis has been described both as an isolated condition and in association with hypothyroidism. These disorders are believed to be secondary to autoantibody reduction.[54,55]

Infants were selected for inclusion in this study because of identifiable ocular abnormalities, either at birth or shortly thereafter. Only 1 CRS patient was first examined at a later age (age 8) and included in the study (Case 3, Fig 21). The major ocular defects observed were cataracts, microphthalmia, glaucoma, iris hypoplasia, nystagmus, strabismus, and variations in the corneal transparency. Every infant in this study had an ocular defect, and from previous reports it is known that with rare exception, ocular defects occur only in combination with other rubella-related defects. Since abnormalities of ocular development are usually found in conjunction with defects of hearing, mental retardation, or cardiac anomalies, it is not surprising that our study population reflects these same occurrence rates. Thirteen of 34 cases (38%) in the study had diagnosed congenital heart defects. Five of these infants died before 3 months of age

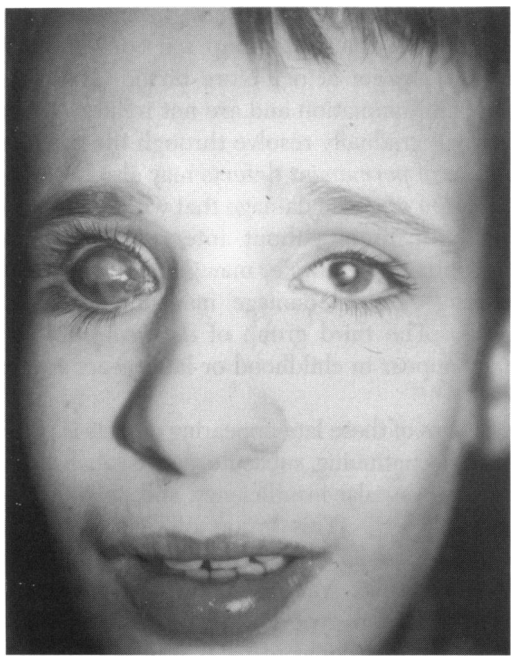


FIGURE 21
Case 3. Preoperative view of grossly abnormal and staphylomatous right eye secondary to multiple operative procedures in infancy and subsequent intractable glaucoma. Enucleation was performed. Boy had congenital rubella syndrome and was first examined and entered the study at age 8. Microphthalmic left eye had dense nuclear cataract and nasal surgical sector iridectomy.

and 1 at 16 months. It is probable that other infants also had cardiac defects that were asymptomatic at the time of initial testing.

Many infants exhibited multiple ocular defects. The history of case 26 was representative of many CRS infants. This infant was born in California weighing 5 lb following a 38-week gestation. A congenital heart defect was noted at birth, and because the left eye was noted to be slightly larger and the cornea hazy, there was initial concern of infantile glaucoma. Intraocular pressures were noted to be minimally elevated in each eye, and it was noted that there was a "slight cataract in the right eye." When the family relocated to the East coast and the infant was examined at age 8 months (Fig 22), it was noted that the right eye was slightly microphthalmic with a hazy appearance to the cornea. The intraocular pressure ranged between 20 and 25 mm Hg. There was a densely sclerotic nuclear cataract, which was considered to be uniquely characteristic of rubella with a visibly liquefied cortex (Fig 23). The opaque nucleus would move freely within the fluid sac. The left eye was noted to be normal in size without pressure elevation and

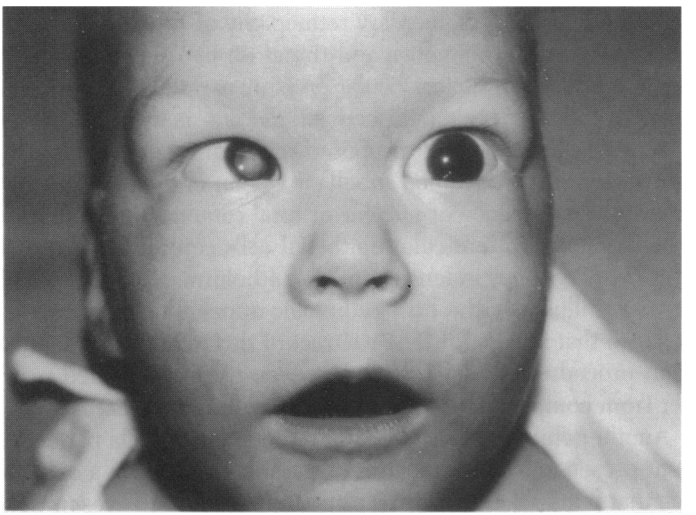


FIGURE 22

Case 26. Eight-month-old infant with culture proven congenital rubella syndrome. Patient presented with unilateral cataract and microphthalmia, strabismus, congenital heart defect, and hearing deficit. (AFIP Neg. 67-5801.1)

Reproduced, with permission, from O'Neill JF. Strabismus in congenital rubella. Arch Ophthalmol 1967;77:450-454.

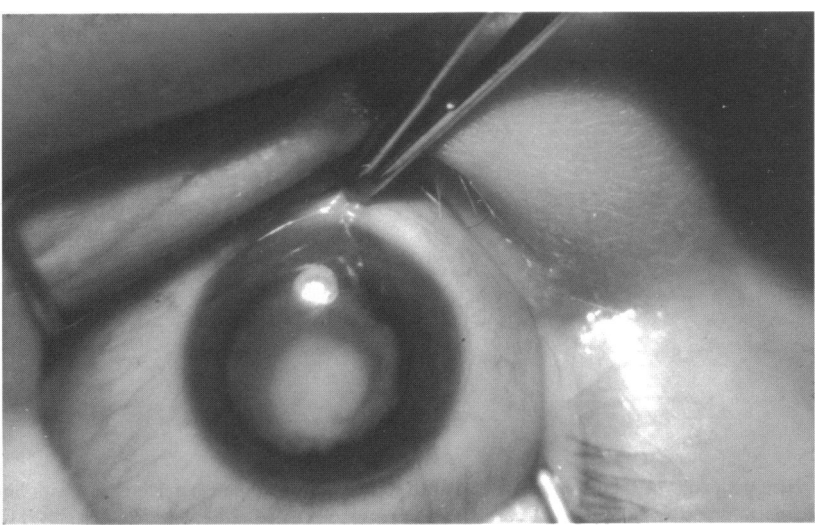


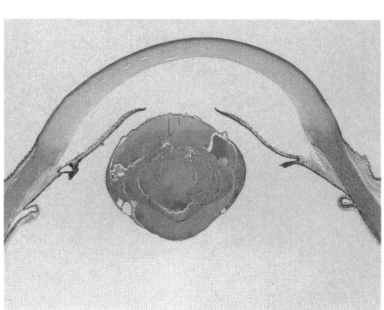
FIGURE 23

Unilateral cataract of infant (case 26) with dense sclerotic nucleus that moves freely in liquefied cortex.

exhibited the typical pigmentary retinopathy of rubella. Rubella virus was isolated from the conjunctiva and throat on two separate occasions. Over several weeks, both the intraocular pressure and the hazy appearance of the cornea of the right eye diminished and did not recur.

In 1968, Zimmerman[22] proposed minimal criteria for the histopathologic diagnosis of congenital rubella infection in the eye. One of those criteria was the presence of nuclear or total cataract with retention of karyorrhectic nuclei in lenticular epithelial cells centrally and the absence of noteworthy changes in lens capsular epithelium. Figs 24A and 24B from that study illustrate the histopathologic appearance of a rubella cataract similar to that in case 26. The cataract of this infant was operated by aspiration procedure at age 1 year; however, the patient died many months later from complications related to congenital heart disease.

Another characteristic of ocular infection in rubella patients is the frequent presence of abnormalities of the iris. It has been a common experience that pupil dilation is often difficult to achieve in eyes in CRS. Gregg[1] first noted that some irides have an atrophic appearance. Both clinical and histopathologic observations have confirmed this, and Zimmerman has convincingly demonstrated that in some areas, there is virtually no iris stroma anterior to the pigment epithelium. Poor development of the dilator muscle fibers is often observed histopathologically.[22] Gregg's observations that some rubella patients had "a sensitivity to atropine" was probably a dose-related response due to the difficulty obtaining mydriasis.[1] Fig 25 illustrates the extreme presentation of this defect in case 32 with a markedly hypoplastic and atrophic iris and cataract in this microphthalmic eye. Iris tissue with this degree of fragility obviously complicates cataract



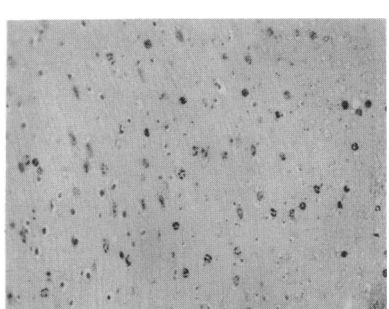


FIGURE 24 A

Histopathology of rubella cataract, similar to Fig 23, shows tumid cataractous lens with liquefaction and vacuolization of cortex and sclerosis of nucleus (hematoxylin-eosin × 11). (AFIP Neg. 65-3996)

FIGURE 24B

Higher magnification demonstrates retained karyorrhectic and pyknotic nuclei characteristic of rubella cataract (hematoxylin-eosin × 350). (AFIP Neg. 65-5251)

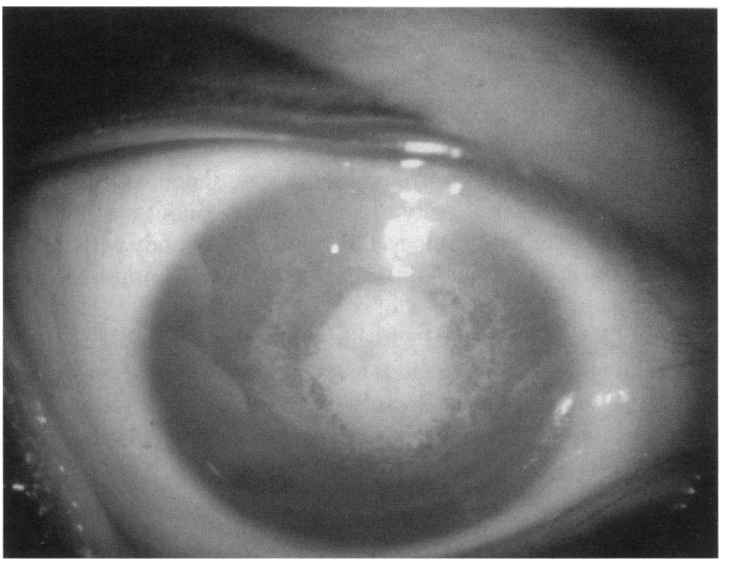


FIGURE 25
Case 32. Markedly hypoplastic and atrophic iris with cataract in culture-proven congenital rubella syndrome.

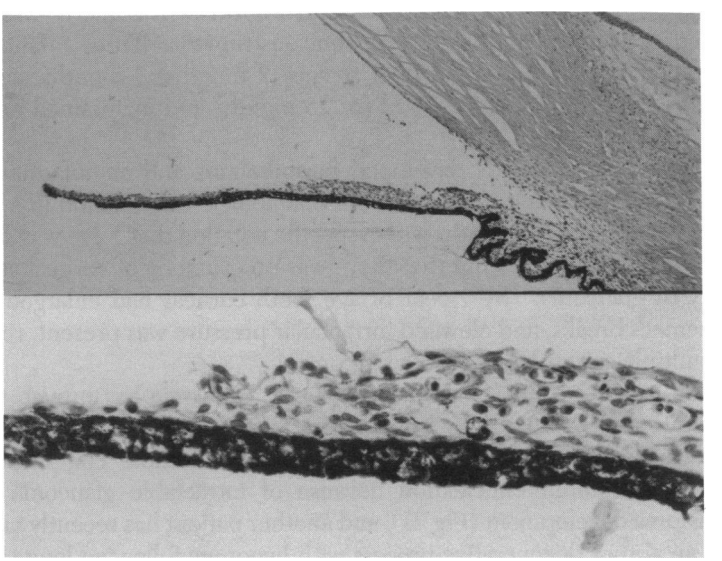


FIGURE 26
Severe stromal atrophy with absence of dilator muscle and incomplete cleavage of anterior chamber angle (hematoxylin-eosin × 350). (AFIP Neg. 65-3974)

surgery in these infants. Fig 26 from Zimmerman's series illustrates severe stromal atrophy in a similar but less severe case.

Figure 27 illustrates the diffuse and irregular deposition of pigment scattered throughout the posterior pole of the retina. This has been described as "salt and pepper" appearance, and Fig 28 in a dual photomicrograph reveals the marked irregularity in size, shape, and melanin content that disrupts the continuity of the retinal pigment epithelium layer. Fig 29 depicts the chronic iridocyclitis in the ciliary body with an isolated area of focal necrosis, which constitutes another of Zimmerman's criteria for the histopathologic diagnosis of congenital rubella.

Correlation of this clinical and histopathologic material is presented because of the major complications associated with the intraoperative and postoperative course of cataract surgery in infants with CRS. Surgeons who were responsible for the care of these infants encountered numerous operative challenges and postoperative complications, as is evidenced by the following observations.

The incidence of glaucoma in congenital rubella varies greatly among studies.[12,60-62] In this select population, 11 patients were found to have elevated intraocular pressure or glaucoma on initial evaluation. Repeated examinations over several weeks noted that 4 patients with microphthalmic eyes (3 bilateral and 1 unilateral) presented early with corneal haze and elevated intraocular pressure, which spontaneously cleared over several weeks (cases 18, 25, 26, 34, and Fig 5A). Tonometry was performed utilizing a handheld applanation instrument. Three infants had congenital heart disease and died at ages 2 months, 3 months, and 16 months. One child was observed for 18 months and maintained normal intraocular pressure.

One patient (case 7) developed buphthalmos and an infantile-type glaucoma. This infant underwent ophthalmologic examination in a birth defects clinic at age 6 months with a specific notation that 1 eye was slightly larger than the other but that there was no evidence of corneal abnormality or glaucoma. By 1 year of age, both corneas had enlarged with Descemet's breaks, and elevated intraocular pressure was present, requiring multiple surgical procedures for control.

The long-term management of aphakic glaucoma has proven to be most difficult. Six patients who had early surgery for bilateral rubella cataracts eventually developed glaucoma with multiple complications. Two eyes required enucleation because of intractable glaucoma with staphyloma development (Fig 21), and another patient has recently undergone an abrupt degenerative process with hypotony following long-standing intraocular pressure elevation and development of a large scleral staphyloma. This eye has also been chronically inflamed, suggesting persistence or recurrence of viral infection (case 4, Fig 30). Another patient

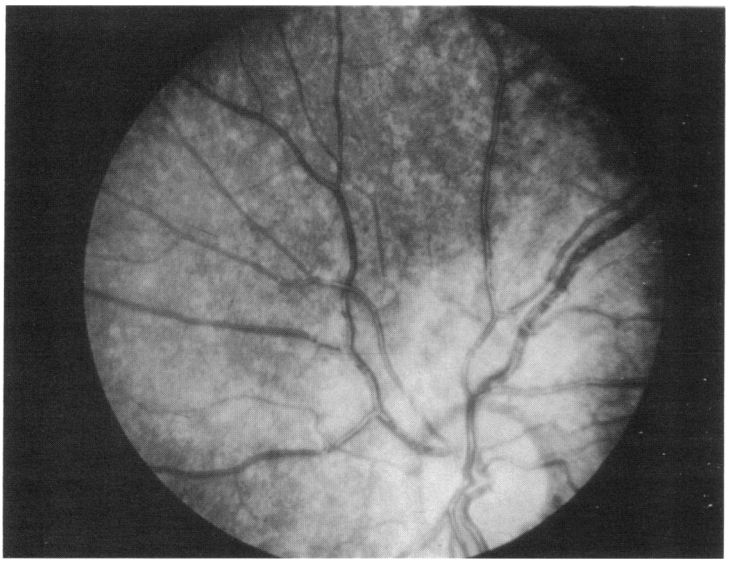


FIGURE 27
Characteristic pigmentary retinopathy of congenital rubella syndrome. Diffusely scattered "salt and pepper" pattern of irregular loss of pigmentation, pigment migration, and clumping. (AFIP Neg. 67-5801-6)

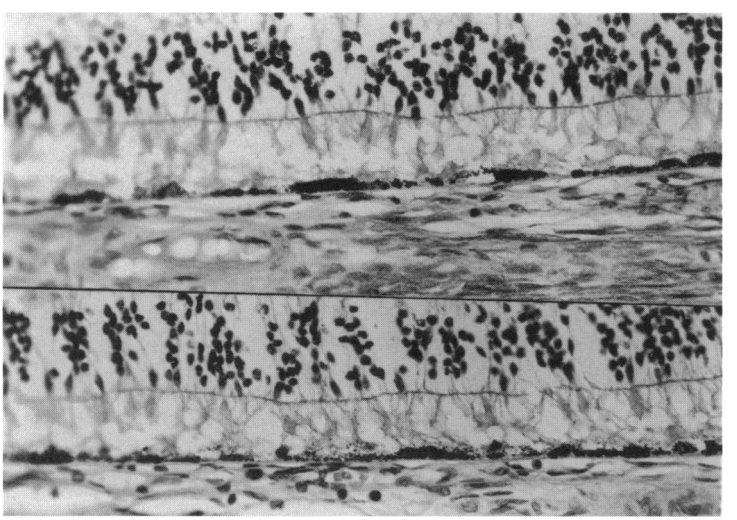


FIGURE 28
Dual photomicrograph revealing marked irregularity in size, shape, and melanin content of retinal pigment epithelium (hematoxylin-eosin × 380). (AFIP Neg. 65-3970)

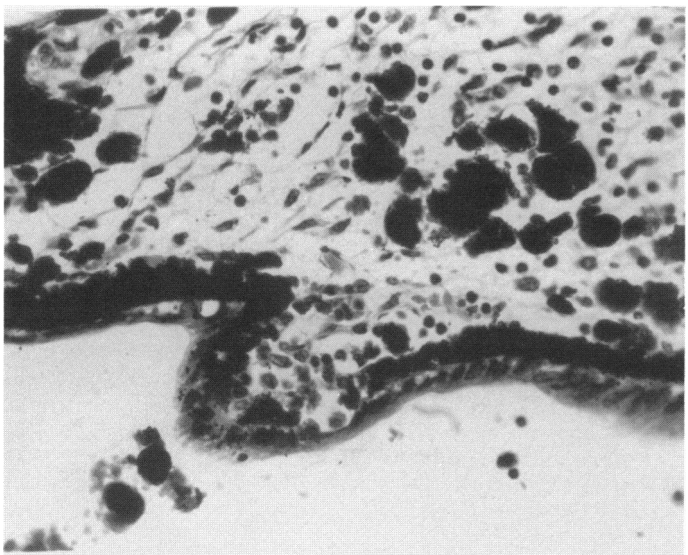


FIGURE 29
: nongranulomatous inflammation with focal necrosis of pigmented epithelium of cil-
ly (hematoxylin-eosin × 380). (AFIP Neg. 65-3970)

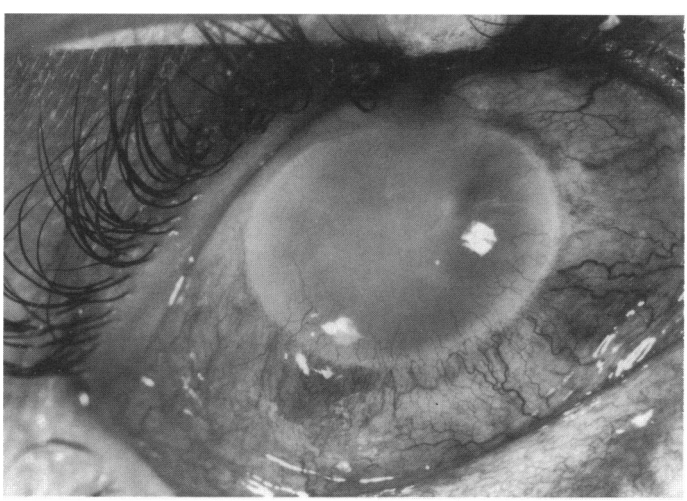


FIGURE 30
Case 4. Right eye following prolonged period of elevated intraocular pressure and earlier bulging scleral staphyloma.

with long-standing glaucoma developed bullous keratopathy, which required 2 separate penetrating keratoplasties (case 5).

Delayed-onset glaucoma in rubella patients following early cataract aspiration has been reported in many series, and the longer the period of follow-up, the greater the possibility that an increase in intraocular pressure may be a complication.[12,54-56,58,63] Chrousos and colleagues,[63] in reviewing 392 consecutive childhood cataract surgical procedures, found a 6.1% incidence of glaucoma. A preponderance of these cases, however, were in patients operated early by a manual aspiration technique. In Wolff's large prospective series,[12] 15 of 328 patients (4.5%) had clinical evidence of glaucoma, through a follow-up of 7 years. Glaucoma was bilateral in 14 of the children, and 11 eyes were buphthalmic. Wolff also noted that 5 patients with cataracts (4 bilateral) had glaucoma; however, no details are presented regarding surgical status. Boger and associates[56,64] reported glaucoma occurring in 13 patients between ages 3 and 22, and all except 2 were in microphthalmic eyes which were aphakic following either cataract aspiration or spontaneous lens absorption.

Important Association of Glaucoma as a Delayed Complication Following Early Manual Cataract Aspiration

Several coexisting factors are contributing causes of glaucoma in aphakic eyes following surgery for rubella cataracts. These eyes are almost universally microphthalmic, with an underlying chronic nongranulomatous iridocyclitis, and many are considered to be harboring viable viral agents. The operative techniques commonly used in 1964 or 1965 would be considered quite primitive by today's standards.[65-67] Surgical manipulation of these eyes almost universally stimulated a chronic and prolonged inflammatory reaction with both anterior and posterior synechiae, mild corneal inflammation, and secondary membrane formation. The need to perform several discission procedures for secondary membranes or more involved capsulectomy procedures was common. Several surgical centers reported a significant number of eyes lost to chronic inflammation and eventual phthisis.[65,68]

An analysis of the surgical techniques prevalent at that time for the removal of infantile cataracts is relevant. Operating microscopes were only becoming available in the early 1960s, and some respected surgeons were still using magnifying loupes for congenital cataract surgery. This was almost 10 years before the availability of irrigation/aspiration, mechanical suction cutting, or phacoemulsification instrumentation. The aspiration procedure as described by Scheie was in general use[65]; however, rubella eyes dilated poorly and required a large basal or sector iridectomy. Attempts to completely remove all of the equatorial cortex in these microphthalmic eyes presented a challenge.[65-67] The presence of live virus

in the cataractous lenses of rubella patients had been conclusively demonstrated in addition to chronic inflammation of the iris, ciliary body, and even possibly the retina.[22,61] A deep anterior chamber at the end of the procedure was generally accomplished by the insertion of an air bubble, and a shallow or flat anterior chamber post-operatively was frequent and contributed to the formation of anterior synechia and angle closure.

The presence of glaucoma and the complications of multiple surgical interventions in the six patients in our series are not unexpected in the presence of chronic inflammation, possible viral persistence, and the technical problems faced in their early surgery. It is probable that many similar complications would exist in the number of patients who were lost to follow-up in this series.

STRABISMUS

The frequent presence of strabismus has been well documented in the congenital rubella syndrome.[54,55,60,69] In addition to the visual loss associated with cataracts and nystagmus, another contributing factor was the presence of microphthalmia in many infants and its related high degrees of hypermetropia (19-28 diopters). Deviations were most always convergent, increasing in frequency with advancing age and some becoming exotropic. Because of the generally poor vision and frequent mental retardation, satisfactory treatment of the strabismus was rarely achieved.

TOXOPLASMOSIS

Recruitment of this series of patients with documented congenital toxoplasmosis varied considerably from those with culture-proven rubella. The youngest toxoplasmosis patient was examined at birth after fetal abnormalities had been detected on routine sonography in the fifth month of gestation. Six other infants were examined in the first year of life; however, the majority (67%) presented and were initially examined with confirmation of the diagnosis after their first year, and 8 (38%) were initially examined and included in the study between age 4 and age 8 years. The specific reasons these children presented for examination are summarized in Table IX. Most were noted to have poor visual acuity in at least 1 eye, which also undermined the stability of their binocular control system and predisposed to the onset of strabismus.

Except for the most severely affected infants who were exposed to infection very early in gestation and suffered a combination of extensive central nervous system and ocular inflammation, the primary ocular defect in this study series is retinochoroiditis. In human ocular toxoplasmosis, the characteristic lesion is a focal necrotizing retinochoroiditis, and the diagnosis of congenital toxoplasmosis relies on the presence of such lesions with serologic confirmation in the infant and mother.[31,32,39,43]

TABLE IX: PRESENTING SIGNS OR SYMPTOMS OF PATIENTS WITH CONGENITAL TOXOPLASMOSIS: REASON FOR INITIAL OPHTHALMOLOGIC EXAMINATION

CONDITION	NO.	REMARKS
Strabismus	10	Ages: 3 mo - 4 yr Esotropia - 8 Exotropia - 2
Nystagmus/strabismus	2	Ages:- 5 mo, 14 mo Esotropia - 2
Early central nervous system abnormality	2	Prenatal hydrocephaly diagnosis Age 3 mo - microcephaly
Failed vision screening	4	Ages: 4 - 8 yr
Routine exam	2	Ages: 4, 6 yr
Other: torticollis	1	Age: 2 yr

It is apparent that strict microbiologic criteria would require most diagnoses of ocular toxoplasmosis to be considered "presumptive," since it is not possible to either isolate or culture organisms directly from intraocular lesions or to demonstrate organisms in histopathologic section in newborn infants. Clinical, laboratory, and pathologic experience, however, has amply documented that the presence of retinal lesions with an appropriate morphologic appearance and a recognized clinical course with serologic confirmation in an infant and mother is sufficient to accept these presumptive diagnoses as positive.[31]

T gondii is probably the most common organism to infect the retina worldwide and has been estimated to cause 35% of the cases of chorioretinitis in the United States and central and western Europe.[23,26] Since acquired toxoplasmosis is not usually accompanied by chorioretinitis, it is thought that most cases diagnosed at any age are related to prior congenital infection. Those beyond the neonatal period probably result from either a recurrence of congenital infection, reactivation of satellite lesions, or the delayed onset of new foci of infection.[24,31,32,43]

The majority of infected infants are asymptomatic and do not have clinical signs at birth but may develop one or more sequelae of the congenital infection later in life. Our use of the term "congenital" therefore refers to both the clinical and subclinical, or latent, cases. Those recognized and identified prenatally or early in neonatal life are usually the most severely affected.

Approximately 50% of untreated women who acquire toxoplasma infection during gestation transmit the parasite to their fetuses; the incidence of transmission is least early in gestation and greatest late in gestation[32,43,70] (Table X). These figures emphasize that although the transmis-

TABLE X: OUTCOMES FOLLOWING TRANSMISSION OF MATERNAL TOXOPLASMOSIS TO THE FETUS[32,43,70]

	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Fetal infection rate	15%	30%	60%
Severe fetal infection	41%	8%	0%
Fetal/neonatal death	35%	7%	0%

sion rate is least in the first trimester, infection acquired early in gestation is more likely to produce severe fetal manifestations. The rate of stillbirth and perinatal death is as high as 35% in the first trimester, and of those live-born, 41% may have severe disease and 24% may have either mild or subclinical signs of infection. In contrast, it is rare to have a severely infected infant first exposed to maternal infection late in gestation, and the subclinical group may be as high as 90%.[70] The small group of infants more severely affected early in gestation will usually have signs of disseminated infection (Table XI). The ocular defects will often include extensive retinochoroiditis with vitreitis and, less commonly, microphthalmia. The systemic signs of diffuse parasitemia often include extensive central nervous system damage resulting from meningoencephalitis and include hydrocephaly, microcephaly, varying degrees of brain damage with mental retardation, and seizure disorders. More than 80% of infants with untreated congenital toxoplasmosis that is clinically apparent in the first year of life had IQs of less than 70, and many had seizure disorders and severely impaired vision.[40]

TABLE XI: MAJOR CLINICAL MANIFESTATION OF CONGENITAL TOXOPLASMOSIS[32,70]

CENTRAL NERVOUS SYSTEM	EYE	OTHER ORGAN SYSTEMS
Meningoencephalitis	Retinochoroiditis with macular predilection	Hepatomegaly
Hydrocephalus	Microphthalmia	Splenomegaly
Microcephalus	Iridocyclitis	Jaundice
Focal cerebral necrosis	Vitreitis	Fever
Focal cerebral calcification	Traction retinal detachments	Thrombocytopenia
Seizure disorder	Papillitis	Petechiae/purpura
Severe brain damage	Nystagmus	Maculopapular rash
Mental retardation	Strabismus	Anemia
Spasticity	Cataracts	Nephrotic syndrome
Palsies	Phthisis bulbi	Myocarditis
Developmental disabilities	Blindness	Pneumonitis
Learning disorders		Immunoglobulin depression
		Bony metaphyseal abnormalities
		Deafness

Other structures and organ systems affected by early and extensive disseminated infection include hepatosplenomegaly, thrombocytopenia, skin, heart, bony abnormalities, and deafness (Table XI).

It has been estimated that between 3,000 and 4,100 of the 4.1 million infants born annually in recent years in the United States are afflicted by congenital toxoplasma infection.[27,32,39,41,59] Between 80% and 92% of congenitally infected individuals not treated as infants develop chorioretinal lesions by adolescence,[21,27,41] and Mets and associates[27] have aptly termed this a recurrent, relapsing, and progressively destructive ocular disease.

The Organism and Transmission

T gondii is a unique and highly virulent organism, which in its free proliferative form is rapidly invasive and destructive. It is an obligate intracellular protozoan parasite, occurring in many mammals and man, which causes a variety of illness previously thought to be due to other agents or of unknown cause.[32] Organisms exist in three forms or stages: (1) a proliferative stage, or tachyzoite; (2) a tissue cyst, the latent or dormant form which contains bradyzoites; and (3) the oocyst, a reproductive form that occurs exclusively in the intestinal tract of members of the cat family.[25,32,43]

Tachyzoite form. Except perhaps for nonnucleated red blood cells, the tachyzoite can invade all mammalian cells, particularly phagocytes. After penetration, it quickly multiplies, ultimately causing disruption and death of the host cell.[32,43] During the initial stage of infection, parasites are present mainly as tachyzoites. Their invasion of host cells is a rapid event, taking 15 to 40 seconds (one quarter of the time required for phagocytosis), and involves complex mechanisms that combine aspects of phagocytosis with those of active invasion[25,71] (Fig 31). The tachyzoite cannot withstand freezing and thawing, desiccation, or exposure to gastric or duodenal digestive juices, so rapid penetration into host cells is necessary to provide its protection.[43]

Bradyzoite Form. When the host develops its initial, nonspecific immune response and begins to recognize the organisms as foreign, the proliferative or invasive stage diminishes and the infection reaches a latent or chronic stage with bradyzoite formation and the persistence of *T gondii* in multiple tissues of the body months or years after initial infection.[72] Once they rupture, however, they release organisms or other antigenic products, which excite vigorous inflammatory responses in the retina and choroid. The severity of infection is probably a combination of the strain virulence and host susceptibility. In the eye, active infection begins in the retina with severe inflammation, necrosis, and exudation into the vitreous. Multiple foci generally occur, and secondary involvement of the choroid is always present with both tachyzoites and cysts throughout these lesions.[13-16,31]

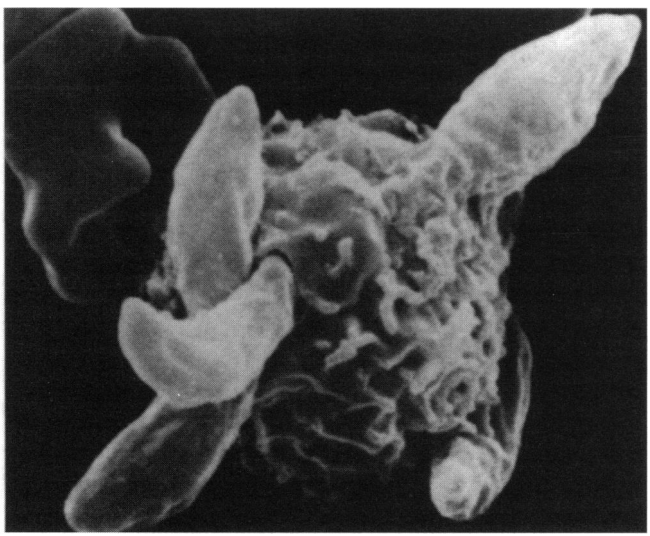


FIGURE 31
Scanning electron micrograph depicting invasion of mouse peritoneal macrophage by Toxoplasma tachyzoites (X 14,000).
Photo by Mary Louise Chiappino. Reprinted, with permission, from Tabbara KF: Ocular toxoplasmosis. In: Tabbara KF, Hyndiuk RA. Infections of the Eye. Boston: Little Brown; 1995:659-672.

The Oocyst Form. The oocyst form is found only in the feces of members of the cat family, the definitive host for *T gondii*. The oocyst is far more resistant than other life-cycle forms and can survive for months in water and for a year or more in moist soil.[32,43] Ingestion of sporulated oocysts transmits the infection. The cysts are destroyed by high temperatures in cooking, and the common practice of freezing commercial meats and the use of home freezers both have a beneficial effect in destroying cysts. Epidemiologic estimates are that about 8% of commercial beef, 20% of commercial pork, and 25% of commercial lamb contain encysted toxoplasma bradyzoites.[39,43]

Specific Vulnerability of the Central Nervous System and the Eye
The predominant tissue involvement and site of persistence of tissue cysts appears to be in skeletal muscle in most animals. In humans, however, there is a predilection for involvement of the central nervous system and the eye. Of the several factors which influence this selectivity, the most important seems to be the limited availability of antibody in these 2 neural structures.[25,45] The barrier to passive diffusion of antibodies to the brain and eye has been given as an explanation for the continuing proliferation

of the parasite in these sites while they are disappearing from extraneural sites. Continued tissue destruction may occur in those sites where ready access to circulating antibody is impeded.[32] The second important factor contributing to the apparent vulnerability of the eye and brain is the lack of ability of these tissues to regenerate, thus promoting more severe or extensive permanent damage.

The optic nerve may be affected, either primarily or secondarily.[73] O'Connor comments on and questions a theory that the optic nerve may be a principal route by which organisms gain access to the retina noting that many lesions thought to arise from the nerve are considered to be of juxtapapillary origin.[31]

Segmental atrophy of the optic nerve characterized by pallor and loss of substance, especially of the temporal portion of the nervehead, is presumably due to retrograde degeneration of a significant number of nerve fibers that extend through the papillomacular bundle. This segmental atrophy reflects the death of retinal ganglion cells (Figs 15, 16, 20G, and 20J).

Late Manifestations of Ocular Toxoplasmosis

Several reports of long-term follow-up of ocular lesions in toxoplasmosis suggest that the persistence of dormant organisms in tissue cysts in the eyes, brain, and possibly other organs may be present over a lifetime. Rao and Font[72] reported an 82-year-old man with bilateral recurrent toxoplasmic retinochoroiditis whose one eye became painful and blind and was enucleated. Histopathologic sections revealed multiple retinal cysts, some of which appeared necrotic but others which appeared viable with numerous organisms in adjacent areas. Specific immunofluorescent methods detected antigenic material to the toxoplasma organisms.

Wilson and colleagues[41] found that almost all of 24 children with documented congenital toxoplasmosis who were initially asymptomatic at birth developed signs of recurrent retinochoroiditis by an average age of 8.5 years, and a high percentage of these children were noted to have decreased intelligence. In a recent study of infants treated over a 1-year period with pyramethamine and sulfa, Mets and coworkers[27] found a recurrence of retinochoroiditis in 13% of the treated infants and 44% of a previously untreated historical control group. New lesions were often noted to be contiguous with old lesions but also occured in areas previously noted to be normal retina. In a 20-year follow-up study of congenital toxoplasmosis including both treated and untreated infants, Koppe and associates[74] found that of 11 congenitally infected children, 9 developed previously unnoted scars in one or both eyes.

It is apparent that toxoplasma organisms remain dormant but in a viable form in the eye and brain and have the potential of reactivating

over long periods of time following initial infection. Specific antimicrobial treatment may hasten the reversal of active infection but does not appear to affect the encysted organisms, which have the potential for reactivation.[27]

UNKNOWN CAUSES OF OCULAR DEFECTS OF INFECTIOUS ORIGIN

Figure 32 depicts a chorioretinal lesion with central atrophy, a deeply pigmented border, and a vitreal band extending to the optic disc. This lesion strongly resembles the clinical appearance of toxoplasmic retinochoroiditis, particularly the large lesion in the left eye of Fig 20. All serologic testing, however, has been negative for the known causes of retinal infection, and there have been no clinical signs to indicate other disease processes.

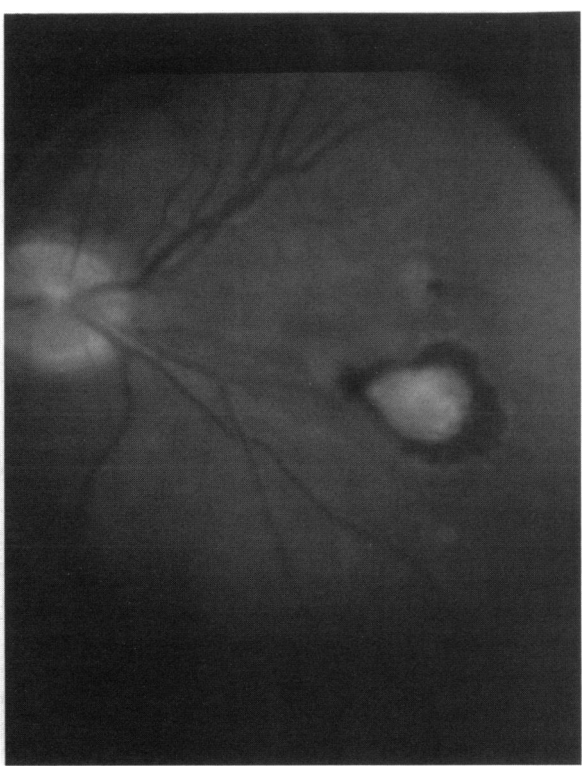


FIGURE 32

Retinal lesion of unknown etiology. Chorioetinal lesion with central atrophy and deepy pigmented border with vitreal band extending to optic disc and several small hypopigmented proximate lesions. Strongly resembles toxoplasmic retinochoroiditis but all serologic studies negative for known causes of congenital infection.

This remains a lesion of presumed infectious origin of unknown etiology.

Keith[75] presented 5 children with chorioretinal lesions, cerebral defects, and negative Sabin-Feldman dye test for toxoplasmosis. He discusses the possibility of other infectious causes of these oculocerebral disease processes and also the possibility of toxoplasmosis existing in the presence of a negative dye test. Overall[3] states several important reasons to explain why viruses are probably the causative organisms for the approximately 80% of congenital malformations that appear to occur on an infectious basis but remain of unknown cause. Although we have learned much about the causes of the ocular defects of congenital infection, diagnostic dilemmas remain to stimulate continued investigation.

CONCLUSIONS

In addition to significant visual impairment and blindness, congenital infection causes major fetal damage, including malformations and chronic disease in the newborn, which may persist and recur throughout life. The devastating effects of the last major rubella epidemic, which occurred more than 30 years ago, continue in the survivors. Those least affected may have severe hearing deficits, while many have persisting cardiac disease, major psychomotor retardation, and other late-onset conditions still being identified. Numerous ocular defects persist as continuing problems related to early infection, reactivation, and late-onset complications. Although effective vaccination programs have essentially eradicated rubella as an epidemic threat in this country, congenital toxoplasmosis continues to affect between 3,000 and 4,100 infants each year; many more subclinical infections proceed undetected. Significant reduction of this number could occur with identification of susceptible seronegative women in early pregnancy and effective counseling programs about the sources of infection. A program of antimicrobial treatment for pregnant women exposed to *T gondii* appears to provide a reduction of fetal injury.[42] Studies in France have confirmed a significant reduction of neonatal morbidity in congenital toxoplasmosis with such an identification and treatment program; however, little progress has been made in this country toward the development of such programs, nor will an effective vaccine be available for many years.

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