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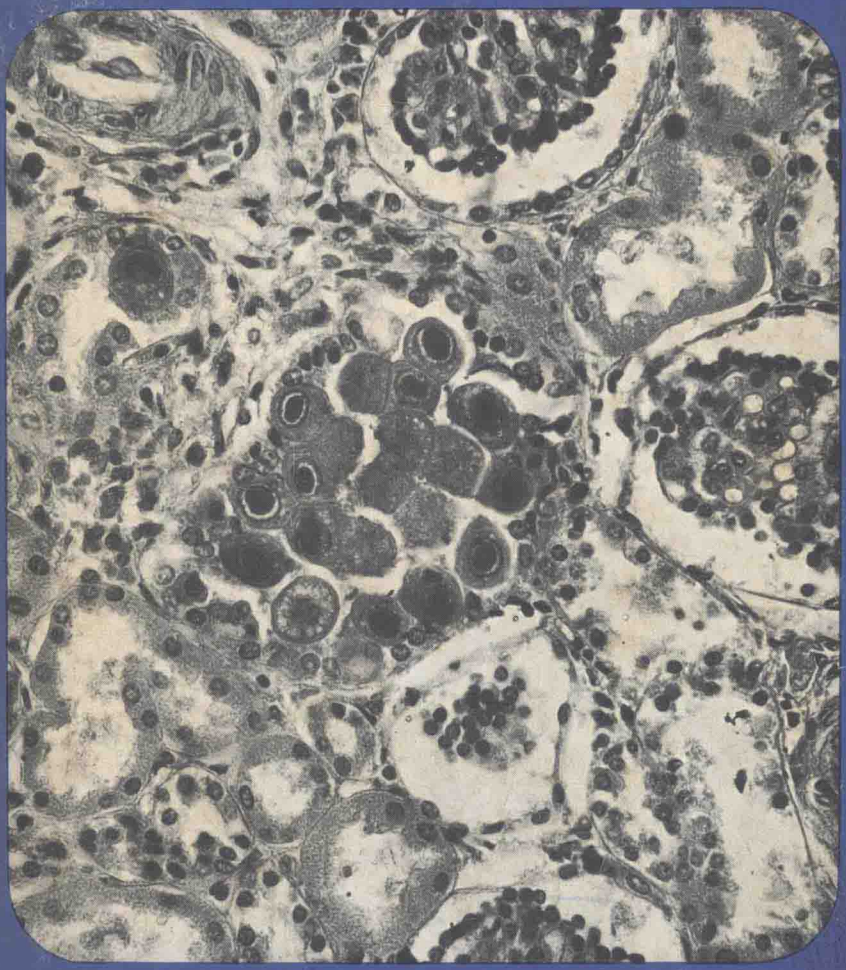
VIRAL INFECTIONS of the HUMAN FETUS



VIRAL INFECTIONS OF THE HUMAN FETUS

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This book is dedicated to Beatrice, Reza, and William.

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Preface

The medicine we practice is as good as our understanding of the series of events and processes that combine to produce disease. This book attempts to bring together epidemiology, clinical virology, and pathology and to link these fragments of knowledge in a meaningful, coherent manner so as to delineate the probable pathogenesis of those viruses that are capable of establishing infection *in utero* and influencing perinatal morbidity and mortality.

Presently, understanding of the natural history of the disease process caused by a given virus is all too often the sole weapon in our armamentarium. Yet it is fundamental to the practice of the highest pinnacle of our art, preventive medicine. With the commitment of the science of medicine to the eradication of disease, we will see the successful development of more effective antiviral drugs. Initially, the narrow therapeutic indexes will demand a thorough understanding of the disease process in which they are to be used.

This monograph makes no pretense of being a text of virology or pediatrics. However, it does attempt structurally to span a void in our knowledge. The text is potentially didactic for obstetricians, pediatricians, and neonatologists. It is hoped that it will aid in putting personal experience in the realm of congenital viral infections into a meaningful perspective, which, in turn, will stimulate individuals to fill in the knowledge gaps.

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G. R. G. M.

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Contents

1

GENERAL PRINCIPLES

Viral Infections of the Human Fetus

Certain viruses have the ability of establishing concomitant disease in both the gravid female and the products of conception. Infection of mother and fetus, though caused by a common etiological agent, may vary significantly in manifestations and outcome in the respective hosts. An innocuous infection in the adult host may result in a fulminating and possibly lethal entity in the developing embryo or fetus. As yet there are no valid statistics that transcribe viral infections of the developing embryo and fetus in terms of fetal wastage, perinatal mortality, and anomalous somatic development. Nevertheless, advances in virology have lent significant insight into the pathogenesis of transplacental viral infections and their ramifications in these areas.

THE PLACENTA

Transplacental viral infection probably involves the placenta either as part of widespread hematogenous dissemination to the products of conception or, sequentially, as the prime focus of invasion. When sought for in placental tissue, in many instances virus may be recovered;[1-13]* however, knowledge concerning placental involvement is, at best, fragmentary and has been primarily retrospectively attained. Except for the stigmata of intranuclear inclusion bodies produced by certain DNA viruses, histologic assessment of the placenta for evidence of viral involvement is inadequate, because of either the absence of visible cytopathic effect and its resultant inflammatory response or the difficulty of distinguishing these focal changes from the involutional changes which occur during the third trimester. Consequently, a proper prospectus of placental involvement in transplacental infection is contingent upon recovery of the virus. Unfortunately, there are almost no prospective virologic studies in this area.

Because transplacental infection implies hematogenous dissemination from the maternal circulation, a virus must first be capable of inducing viremia in the maternal host. However, not all viruses capable of viremia in the maternal host traverse the placental barrier, nor do those viruses that can traverse the barrier do so with regularity. The complex of factors regulating this phenomenon is poorly understood. Until the pathogenesis of rubella virus was adequately delineated, it was presumed that placental involvement was merely a consequence of hematogenous dissemination. However, it has been shown for rubella virus that it is only when the virus is able to establish infection beyond the placenta that the virus produces its teratogenic effect.[1-2] Data emanating from the 1963–1964 rubella epidemic indicated that infection of the placenta was a common phenomenon following

* See References, pages 9–11.

TABLE 1-1

	Ability to Traverse Placental Barrier	Ability to Traverse Blood-Brain Barrier
Coxsackie group B	+	+
Cytomegaloviruses	+	+
Hepatitis virus type B	?	−
Herpesvirus hominis types 1 and 2	+	+
Lymphocytic choriomeningitis	(+)	+
Mumps	+	+
Polioviruses	+	+
Rubella	+	+
Rubeola	+	+
Vaccinia	+	+
Varicella-zoster	+	+
Variola	+	+
Western equine encephalitis	(+)	+

+ Documented by virus recovery.
(+) Inferred from serologic data.

maternal rubella early in gestation, but that dissemination to the fetus was a much rarer occurrence and was contingent in part on the gestational age of the fetus.[2] The factors governing this phenomenon could function either by limiting the spread of virus to the placenta or by preventing infection within fetal tissues. In one case in the literature, maternal infection with rubella virus occurred late in gestation, and virus recovery from the products of conception was limited to myocardium and placenta.[1]

Every virus able to traverse the placental barrier in the adult, with the possible exception of serum hepatitis virus, possesses the ability to traverse the "blood-brain barrier" (Table 1-1). If this parallel is more than an interesting juxtaposition of facts, it is not inconceivable that similar factors may govern both phenomena.

Until the natural history of transplacental viral infections is documented through prospective virologic studies, one is limited to saying that placental infection probably parallels dissemination of the virus to the fetus, though the inverse corollary may not be true.

IMMUNITY—INHERENT AND ACQUIRED

With the exception of certain DNA viruses—e.g., cytomegaloviruses, herpesvirus hominis types 1 and 2, and the herpes zoster-varicella group, which are capable of producing latent infection—viruses in the adult host undergo what is termed *immune elimination,* such that when sought for in biological fluids or tissues they are no longer recoverable and manifestations of virus reactivation do not occur. The establishment of viral infection within fetal tissues does not appear to elicit an entirely comparable response. With rubella virus, once infection is established within the fetus, the virus persists in the tissues throughout the gestational period and beyond into the first year of life. Virus is recoverable from throat washings, urine, cerebrospinal fluid, and tears, but rarely from serum at parturition.[2,14–16] As late as a year after birth virus may be recovered from almost every organ studied. A comparable but more limited phenomenon is inferred or has been demonstrated in congenital cytomegaloviruses, herpesvirus hominis types 1 and 2, vaccinia, and variola.

The time of immunologic responsiveness in the human fetus has been postulated to occur about the twentieth week of gestation.[17] This dating is based largely on the morphologic observation that despite the presence of *Treponema pallidum* within fetal organs, morphologic inflammatory lesions associated with plasmocytoid or plasma cells do not appear until the twentieth week of gestation in congenital syphilis.[17] The combination of delayed tissue responsiveness and the presence of plasmocytoid cells has been interpreted as indicating immunological competence on the part of the human fetus.[18]

In terms of gestational age and production of specific antibodies, immunologic responsiveness in the developing lamb appears to be a partial function of the type of immunogen utilized. Immunologic responsiveness in the fetal lamb occurs at different times in

gestation depending on the antigen used, suggesting that it is not an all or nothing phenomenon, but may involve at least one intermediary stage in which only certain antigens can induce a full antibody response.[19] The immunogen indicating the earliest antibody response in the fetal sheep has been ØX 174 phage, a bacterial virus.[19] If a parallel situation exists in the human fetus, immunologic responsiveness to viruses may occur earlier than the twentieth week of gestation.

Early exposure of the developing embryo to viral antigens does not appear to overwhelm its immunologic capacity and render the embryo immunologically incompetent. When sought for in fetal, cord, and neonatal serum from cases of congenital rubella, specific IgM immunoglobulins are readily demonstrable.[20–23]

Because IgM immunoglobulins of maternal origin are excluded from the fetal circulation, this finding constituted presumptive evidence for the human fetus to respond *in utero* to the antigenic determinants of rubella virus. At two to three months of age infants with congenital rubella do not exhibit a disappearance of neutralizing or hemagglutination-inhibiting antibodies, as would be anticipated if the titers were totally contingent upon transplacentally acquired maternal immunoglobulins.[24,25]

Dancis and coworkers have demonstrated that at about three month's gestation I^{131} labeled gamma globulin is transferred from the maternal to the fetal circulation in low but significant amounts.[26] IgG immunoglobulin levels in human fetuses are low through the fourth month of gestation; thereafter the values increase, equal the maternal values around the ninth month, and, depending upon the mode of delivery, exceed them slightly at term.[27,28,29] Because the titers at term depend primarily upon gestational age, premature infants tend to have lower antibody titers. At birth the newborn infant has in its serum a vast array of specific immunoglobulins directed against viral agents. These antibodies in the neonatal serum are primarily IgG immuno-

globulins. Unless transplacental transmission and infection of the fetus has occurred, they reflect previous maternal experience with these viral agents. (Figure 1-1).

Prior to birth the fetus, in whom transplacental infection has occurred, exhibits a high titer of specific neutralizing antibodies directed against the virus in question. This titer represents a

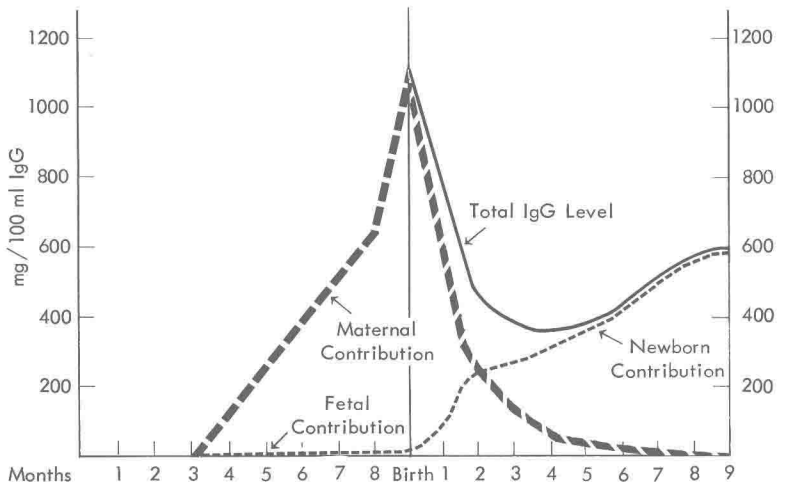

Figure 1-1. A schematic representation of probable development of IgG levels in the fetus and newborn. (Reproduced from M. Allansmith: *J Pediat,* **72:**276, 1968.)

composite of IgG immunoglobulins of maternal derivation and endogenous IgM immunoglobulins. Despite the high titers of specific antibodies and barring the establishment of a latent infection, fetal infection, which may have been present since the first or second trimester, is not eliminated in a manner entirely comparable to postnatal infection. Although the presence of specific antibodies is probably responsible for the infrequency of recovery of virus from the blood in congenital viral infections, it has yet to

be shown that they are capable of modifying the pathological expression of the virus once the infection has been established.

Homologous specific immunoglobulins in the form of hyperimmune serum or gamma globulin are probably as ineffective in aborting infection once it has been established as the "isologous" specific immunoglobulins which develop as a result of infection in the maternal host. Both are subjected to the limitation of selective quantitative as well as qualitative transport by the placenta. For gamma globulin to be effective, therapy must be directed at either preventing infection or modifying the maternal viremia in terms of titer and duration. There is considerable circumstantial evidence to suggest that once infection is established, the administration of specific hyperimmune antibody may not be warranted. It has been clearly demonstrated that endogenous antibody formation may be suppressed by specific exogenous IgG immunoglobulins.[30–34]

DEFINITION OF CONGENITAL VIRAL INFECTION

Prior to the advent of certain virologic and immunologic techniques, congenital viral infection was defined as disease present at birth or developing before the shortest known incubation period for that virus in the immediate neonatal period. Although still a valid documentation of congenital infection, it results in the recognition of but a limited spectrum of disease and excludes those cases of congenital infection whose incubation period is one standard deviation removed.

Congenital infection does not require either overt clinical disease or the presence of histologic lesions. As has been pointed out by René Dubos, "the determinants of the disease are not the same as the determinants of infection."[35] In its most rigid form the definition of congenital infection is the exposure *in utero* of the developing embryo or fetus to the antigenic determinants of presumably infectious virus particles and the subsequent elabora-

tion of specific antibodies of fetal origin. These antibodies are of the IgM type and are more susceptible than maternal IgG antibodies to the degradative effects of mercaptoethanol. Consequently, a proportionally greater reduction in the titer of neutralizing antibody of the cord or neonatal serum over maternal serum would be anticipated after mercaptoethanol treatment. Antigenic stimulation of the fetus *in utero* may result in the

TABLE 1-2 IgM Immunoglobulin Levels at Different Ages

	Cord	One to three months
Stiehm and Fudenberg, *Pediatrics,* **37:**715, 1966	11 + 5 mg/100 ml. range 5–30 mg/100 ml	30 + 11 mg/100 ml range 16–67 mg/100 ml
Thom, McKay, and Gray, *Arch Dis Child,* **42:**259, 1967	Newborns < 2500 g 9.1 mg/100 ml Newborns > 2500 g 10.4 mg/100 ml	

quantity of IgM immunoglobulins detectable in cord or neonatal serum being elevated above the anticipated values (Table 1-2). MacCracken et al. have shown that 25 per cent of infants with congenital rubella syndrome have appreciable elevations of their IgM immunoglobulins.[36] In general, they found a positive correlation between these elevations and the severity of the clinical involvement.

When maternal viral infection occurs in gestation at any time other than the immediate perinatal period, the demonstration of persisting neutralizing or hemagglutination-inhibition antibodies beyond three months of age constitute highly suggestive evidence of congenital infection. Complete documentation of congenital infection is contingent on the recovery of the virus at parturition from presumptive sites of recovery, e.g., placental, products of