Intrauterine Infections

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Contents

Introduction

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The title of this symposium is 'Intrauterine Infections'. This includes infections caused by any microorganism, protozoon, bacterium or virus, and those infections which take place between conception and birth. But we don't need to be too rigid about this; contributors may like to refer to pre-conceptual infections, possibly with rubella at one end of the scale, and perinatal or early postnatal infections at the other. So one need not feel inhibited by the title.

Any scientific meeting or symposium should have a clearly defined object and an equally well defined objective. The object of this meeting is first to discuss the causes of intrauterine infections, and why they have attracted increasing attention from microbiologists and others in the past few years. Is it because we have been so successful in controlling communicable disease that microbiologists are in danger of being without a job, or do intrauterine infections cause serious disease? And if so, what is the extent of the problem? We want to concentrate on current knowledge and future trends without too much emphasis on what has already been published and should be generally known. And we want to discuss in depth methods of assessment and diagnosis of intrauterine infections and their effect on the foetus and the child. Finally, and what is so important, we want to look at the problem from the comparative aspect as well, because so often we can learn from mutual discussion with veterinarians. The objective of the meeting, which follows on from the object, is that if we can find evidence which suggests that a particular agent is responsible for intrauterine infections and foetal damage, steps can be taken to do something about it. For example, there is now quite good evidence that rubella is a disease that is worth preventing, but does this apply to cytomegalovirus infection and to toxoplasmosis?

Two final points will, I hope, illustrate some of the facts that we should have in mind in considering the object of this meeting. I have said that we should

look forward and not back, but if the Chairman's prerogative of breaking a rule occasionally may be allowed, I will quote a paragraph from the late Sir Norman Gregg's first paper on congenital rubella cataract, published in 1941. He had been describing cataracts and heart disease, and went on to say 'it is difficult to forecast the future of these unfortunate babies—we cannot at this stage be sure that there are no other defects present which are not evident now but will show up as development proceeds and the possibility of neurotropic manifestations at a later date must be kept in mind'. I feel that, having been associated with this type of research for a number of years, we have been obsessed for too long by looking for defects recognizable at birth. I am sure we have to get away from this and look beyond birth and beyond infancy into childhood for those children who may have been at risk during pregnancy.

The final problem, which I hope we shall discuss in some detail, is to try to define the impact of infections such as influenza and possibly mumps, and the importance of subclinical infections, on the foetus. From time to time these viral agents have been incriminated as a cause of foetal damage, but the proof is lacking. For example, in the case of influenza, it seemed from the Manson report on the study of virus infections in pregnancy (Manson *et al.* 1960) that the outcome to the foetus after maternal influenza was less satisfactory than after chickenpox and mumps, but there was no clearly defined clinical syndrome of defects, but more of a failure to thrive. Recently, Sir George Godber referred to the fact that there was an increase in neonatal mortality some four months after the 1969–1970 outbreak of influenza and a similar increase in 1950–1951. He suggested that this could have been related to influenza in pregnancy. He did not, as has been reported in the press, say that these children suffered from congenital abnormalities, but merely that there was an increase in neonatal mortality. It has also been suggested that in one series under study there is an increase in the incidence of leukaemia in children who were exposed to maternal influenza. Is this true, and if so how can it be corroborated? These are some of the ideas which we might think about during this meeting.

Reference

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The clinical impact of intrauterine rubella

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Abstract The effects of rubella virus on the foetus were first considered to be essentially teratogenic but in the four years following the isolation of the virus in tissue culture in 1962, widespread rubella epidemics occurred in Europe and the USA and a new concept of intrauterine infection was recognized. Infection was shown to persist in the presence of a specific humoral immune response and to cause damage beyond the period of organogenesis. Such damage has since been shown to occur even years after birth. It has also been shown that the foetus, although infected, may escape damage. The spectrum of disease and diversity in age of onset indicate that several mechanisms, singly or in combination, may operate to cause damage.

In the two decades which followed Gregg's reports on the effects of rubella infection in the pregnant woman (Gregg 1941, 1944) it was believed that the virus was essentially a teratogenic agent. It now seems remarkable that the many manifestations, other than deafness, cataracts, congenital heart defects and microcephaly, which were described in patients born following the epidemics in 1963–1964 had escaped or received so little attention until this time. It is possible that a contributory factor was the earlier over-riding concentration on the structural malformations recognizable at birth. The intense interest shown in these patients was undoubtedly due to the development of methods of isolating the virus and of measuring rubella antibody in 1962 (Parkman *et al.* 1962; Weller & Neva 1962). As a result an entirely new concept of the effects of this virus on the foetus evolved, when it became clear that disease affected several systems and damage could occur beyond the period of organogenesis. It was also shown that there was a chronic infection which persisted for weeks and in some cases for many months after birth (Alford *et al.* 1964; Cooper & Krugman 1967), and that the foetus was capable of responding immunologically to the virus (Plotkin *et al.* 1963; Weller *et al.* 1964). These findings permitted the diagnosis of congenital rubella to be confirmed in the laboratory.

The precise circumstances in which foetal infection and damage may occur are not yet clear. However, two factors are apparent. First, infection of the foetus appears to be the consequence of a primary infection, either clinical or subclinical, in the pregnant woman; there is no evidence that reinfection is associated with foetal infection or damage. In support of this contention, congenital rubella has not been observed in a sibling of a patient with congenital rubella other than in twins. The second factor is the age of the foetus at the time of infection. If infection occurs in the first 6–8 weeks of pregnancy there is a far greater risk of damage and of multiple defects than if infection occurs between 8 and 20 weeks. Infection in this later period often results in a single organ being damaged, in particular the inner ear. There is, however, a considerable degree of unpredictability in individual cases. The incidence of damage recognizable at or after birth is of the order of 30–40% for first trimester infection (Dudgeon 1970). It is not certain if infection later in gestation may cause foetal damage, but Hardy and her colleagues (1969) consider that there is some risk up to 24 weeks. In contrast, the incidence of foetal infection is almost certainly higher (Rawls *et al.* 1968; Thompson & Tobin 1970), and infection does not always result in damage (Butler *et al.* 1965; Cooper 1968).

The effects of foetal infection may be presented as in Fig. 1.

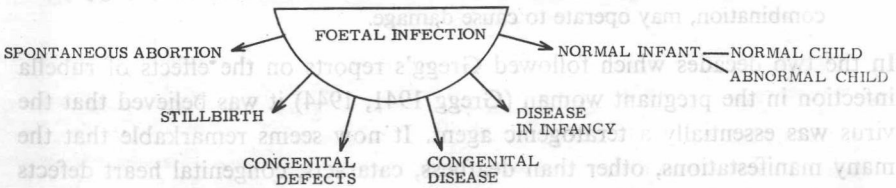

FIG. 1. The possible consequences of foetal rubella infection.

Spontaneous abortion may result from maternal rubella (Manson *et al.* 1960; Lundström 1962; Siegel *et al.* 1966) but the frequency is not known. This is due to lack of accurate data on the incidence of spontaneous abortion from other causes and in part due to the practice of therapeutic abortion in the management of the problem. However, if the foetus survives the infection the pregnancy usually continues to term. Premature delivery is not common and although the pregnancy may end in a stillbirth, this is uncommon even when there is extensive foetal damage.

The incidence of the various clinical manifestations has been reported in several series (Cooper *et al.* 1965, 1969; Korones *et al.* 1965; Plotkin *et al.* 1965, 1967; Rudolph *et al.* 1965; Schiff *et al.* 1971) but in many of these reports the patients have been selected because of the presence of a particular feature

TABLE 1

Congenital heart disease due to intrauterine rubella

Age	*Cardiac lesion*	*Other defects*
6 years	PDA	Bilateral deafness, mental retardation
6 years	PVS, PPAS	Retinopathy, prolonged neonatal jaundice
5½ years	PDA, PVS	Unilateral cataract, bilateral deafness, squint
5 years	PDA, PVS	Unilateral cataract, retinopathy, mental retardation
2½ years	PDA	Retinopathy
1½ years	VSD	Retinopathy, mental retardation
1 year	PDA, PPAS	Bilateral cataracts & deafness, osteopathy, pneumonitis, mental retardation
18 months	VSD	Bilateral cataracts
10 months	PDA	Unilateral cataract, microcephaly, mental retardation, hepatosplenomegaly
10 months	PDA	Bilateral deafness, hepatosplenomegaly
3 months	PDA	Neonatal jaundice, hepatomegaly
10 days	PDA	Pulmonary atelectasis

PDA, patent ductus arteriosus; PVS, pulmonary valvular stenosis; VSD, ventricular septal defect; PPAS, peripheral pulmonary artery stenosis.
(Data of O. Starkova & S. Ebrahim, personal communication 1972.)

and have been examined at a certain age, usually in infancy or early childhood. However, defects of the eye, heart and central nervous system very rarely occur singly and the only one which may occur alone with any consistency is deafness. This is illustrated in the cases reported by Cooper and his colleagues (1969). It was also apparent in a recent study of the viral aetiology of congenital heart disease at the Hospital for Sick Children by O. Starkova & S. Ebrahim (personal communication 1972). They found 12 patients with congenital rubella among 575 cases of congenital heart disease. In all instances, extra-cardiac manifestations were also present in these patients (Table 1). On the other hand, 38 patients had an isolated patent ductus arteriosus. In none of these was there a history of rubella in pregnancy and associated defects occurred in only six, being Down's syndrome, Turner's syndrome, kyphoscoliosis, abnormal facies, hydronephrosis and hypospadias.

Evidence of structural cardiac defects may be present at birth but attention may only be drawn to a congenital heart lesion by the rapid onset of heart failure, when some patients require urgent corrective surgery. Heart failure may also occur in the neonatal period in the absence of signs of congenital heart disease, being due to damage to the myocardium. Histologically there is extensive myocardial necrosis but a striking absence of an inflammatory cell response (Korones *et al.* 1965; Ainger *et al.* 1966). Abnormalities in the ECG

may confirm the myocardial damage but the diagnosis may be one of exclusion.

Stenosis of the pulmonary artery is usually a congenital lesion but rarely it may develop postnatally (Jeresaty & Russell 1967). Multiple stenosis of the peripheral branches of the pulmonary artery may be demonstrable by angiography (Franch & Gay 1963; Rowe 1963; Emmanouilides *et al.* 1964) but such lesions do not usually cause symptoms. It is not known how commonly peripheral pulmonary artery stenosis occurs. In the 575 patients with congenital heart disease of all types investigated at the Hospital for Sick Children, two were found to have stenosis of the peripheral branches of the pulmonary artery, in addition to other cardiac defects. Both were congenital rubella patients (Starkova & Ebrahim 1972). There may also be localized stenosis of other peripheral arteries, such as the renal artery (Forrest *et al.* 1969). It is not inconceivable that major cerebral vessels may be affected in this way but this has yet to be demonstrated.

Although the cataracts in congenital rubella are usually present from birth they may not make their appearance for several weeks. The globe is usually smaller than normal if cataracts are present. Surgery to the cataracts may sometimes be followed by shrinkage and complete loss of function of the eye. It is not known if this is due to the techniques used, to the time of surgery, or to other factors. Virus is frequently recovered from cataractous material at operation. The duration of infection in the eye is longer than at most of the other sites. Virus has been recovered from the eye as late as three years of age (Menser *et al.* 1967*a*).

Other eye defects in congenital rubella include glaucoma, with or without cloudiness of the cornea, but the latter may occur in the absence of raised intraocular pressure (Weiss *et al.* 1966). Retinopathy is also present from birth and is a useful aid to clinical diagnosis. Visual acuity is not normally affected by the retinal changes. Like deafness, the retinal changes may occur as the sole manifestation of congenital rubella.

Hepatomegaly occurring after birth, particularly if there is progressive increase in size, is likely to be due to heart failure. On the other hand, if splenomegaly is also present, which is rarely due to heart failure, the possibility of hepatic disease must be considered. Jaundice, variable in degree, is not infrequent and may be severe and obstructive in type. The histology varies from extensive 'giant cell' hepatitis to focal aggregations of inflammatory cells and bile stasis (Stern & Williams 1966; Singer *et al.* 1967; Esterly & Oppenheimer 1969). There can be marked biochemical evidence of hepato-cellular damage but in our experience the biochemical abnormalities bear no relationship to the severity of the clinical features or to the hepatic histology. Whether there is complete recovery of the liver is not known. Older children usually do

not show either clinical or biochemical evidence of liver disease but it has been suggested that hepatic fibrosis may be a sequel to the neonatal liver disease (Watson 1952).

Thrombocytopenic purpura is another of the features of congenital rubella which is limited to the newborn period (Banatvala *et al.* 1965; Cooper *et al.* 1965; Rausen *et al.* 1967; Zinkham *et al.* 1967). It is present at birth or may appear within a few hours. The lesions, which have a maximal distribution on the head and upper trunk, are well circumscribed, slightly raised, rarely petechial and not ecchymotic. Very occasionally, fresh lesions may appear during the first week, after which the skin lesions gradually fade. Although there may be bleeding from the gastrointestinal tract, bleeding at other sites causing symptoms is unusual. The low platelet count may persist for several weeks but on reaching normal levels it remains normal. Damage to the megakaryocytes is generally considered to be the cause of the thrombocytopenia. A mild haemolytic anaemia may also be present. Hypoplasia of granulocyte and erythrocyte precursors has also been reported (Lafer & Morrison 1966).

Neurological abnormalities may be evident at birth but it is clear that besides prenatal damage, active postnatal disease can ensue. Microcephaly may be present at birth but may become evident only as development proceeds. During the neonatal period and throughout infancy, signs of cerebral palsy, lethargy, restlessness, irritability, seizures and fullness of the fontanelle may occur. The protein and cell count of the cerebrospinal fluid (CSF) may be elevated at the onset but may become abnormal after birth. Virus can be recovered from the CSF for periods up to 18 months (Desmond *et al.* 1967). The ultimate prognosis is difficult to evaluate in these circumstances, particularly if there is associated loss of hearing or vision (Streissguth *et al.* 1970). At autopsy these brains have shown multifocal necrosis, extensive vasculitis and perivascular calcification (Desmond *et al.* 1967; Rorke & Spiro 1967).

Adenopathy may also be present in the neonatal period and is most marked in the occipital and posterior cervical regions; it is very similar to the enlargement of glands in postnatal infection but the enlargement may persist for several weeks. At birth, diagnostic assistance may be obtained from skeletal radiography which can reveal widespread areas of defective ossification in the metaphyseal regions of the long bones and generalized demineralization of the skull bones with delay in closure of the anterior fontanelle (Rudolph *et al.* 1965). However, these bone changes do not persist beyond 3–6 months of age.

Further and often striking features of the congenital rubella infant are failure to thrive, feeding difficulties, slowness to gain weight and persistent or recurrent episodes of diarrhoea. There is also an increased susceptibility to infections and the infant may succumb to pulmonary infection with pneumo-

cystis carinii (Lingeman *et al.* 1967; Phelan & Campbell 1969; M. A. Menser, personal communication 1969). The first year of life is critical for survival. The mortality is between 15 and 20% and may be as high as 35% if thrombocytopenia is present (Cooper 1968).

The significance of the dermatoglyphic abnormalities that have been reported (Achs *et al.* 1966; Alter & Schulenberg 1966) is not clear. We feel that they should not be considered in isolation but should be evaluated with the patterns of the parents and siblings.

From three months of age until the end of the first year several other clinical problems may arise which might be termed 'late onset disease'. Although they are not common and have not received a great deal of attention they may be important in understanding one of the major unsolved problems, namely the cause of the persistent infection. First, patients may develop a generalized rash (Castrow & de Beukelaer 1968). It is not unlike the rash of acute rubella in appearance but in some cases it may have seborrhoeic features and may superficially resemble the rash seen in some types of histiocytosis. It is chronic, lasting many weeks, and may fluctuate in severity. Biopsies of the lesions have shown focal aggregations of round cells in the dermis.

Another form of late onset disease and far more important is a generalized lung disease. The clinical features are cough, tachypnoea, cyanosis and generally a paucity of adventitious sounds. There is a high mortality and at autopsy the lesion is an extensive interstitial pneumonitis (Singer *et al.* 1967; Thorburn & Miller 1967; Phelan & Campbell 1969). In our experience of four patients with this type of lung disease, there has, in all cases, been a dramatic response to ACTH or corticosteroids. The age of onset and the response to steroids, albeit in a very small number of cases, suggested that immunopathological mechanisms may be operating to cause the lung disease. The recently described case of intense lymphocyte infiltration of the pancreas (Bunnell & Monif 1972) could possibly be a similar expression of this phenomenon.

Defective hearing is frequently not suspected at an early age, particularly in the absence of a history of maternal infection or the other defects characteristic of congenital rubella, such as cataracts or congenital heart disease. In addition, there are well-known difficulties in assessing hearing in the young infant. The main lesion is damage to the organ of Corti and we now believe that intrauterine rubella as a cause of this type of hearing loss is more common than was previously thought (5%) and is probably responsible for 20–25% of all cases (Gumpel *et al.* 1971). The true incidence of deafness is difficult to estimate, as patients with unilateral hearing loss frequently escape attention.

Impairment of hearing may also be due to central auditory imperception (Ames *et al.* 1970). A suspicion of deafness may not arise until there is evidence

of delay or impairment of speech. However, some congenital rubella children with speech problems have normal hearing. Intellectual impairment may be the cause of these speech difficulties, but it is also possible that language disorders are a specific defect in congenital rubella (Feldman *et al.* 1971).

Failure to recognize hearing defects in early life could be due to causes other than lack of awareness on the part of the physician or to failure to detect it by clinical examination. Children aged 2–3 years of age, born to mothers with a history of rubella in pregnancy and serological evidence of intrauterine rubella, have had normal hearing and normal speech development, yet some of these patients have been found to be deaf at 6–7 years of age (Peckham 1972). Also it has been the clinical impression of many working with children deaf after congenital rubella that hearing may deteriorate with age, but this has yet to be confirmed by sequential studies.

Some congenital rubella patients exhibit the syndrome of complete autism or possess several of the features of the syndrome (Chess 1971). It is difficult to determine the role of hearing and visual defects in such cases, but occasionally a child with apparently normal hearing and vision is frankly autistic (C. S. Peckham, personal communication 1971).

There have been few longitudinal studies of somatic growth of congenital rubella patients. Michaels & Kenny (1969) showed that most patients remain smaller than average during infancy but grow at a normal rate. In a few there is a growth spurt at the time of apparent termination of the infection; in others there is actually a deceleration of growth. No endocrine basis could be demonstrated in the patients with impaired growth and it was not related to hepatic, cardiac or renal disease. Stunting of growth was more common after maternal rubella in the first eight weeks of pregnancy than after later infection. In seventy of our patients aged 3–19 years, 40% were below the 10th percentile for height and those with more severe multiple defects had a greater retardation of growth.

An important question concerning the older child and young adult is: what are the longterm effects of the intrauterine infection? Is it possible to make an accurate prognosis in early life? Menser and her colleagues from Sydney suggested that the prognosis is not as poor as might be believed by citing the relatively good adaptation of a group of 25-year-old patients, which was considerably better than the predictions in early life (Menser *et al.* 1967*b*). The considerable improvement in neonatal care in recent years, particularly in the field of neonatal cardiac surgery, makes survival of more seriously affected infants more likely. In our patients we have found that the presence of deafness and bilateral cataracts makes normal educational development very unlikely (Gumpel 1972). Another major factor in the early assessment of the outlook

for these patients is the development of signs of damage at periods after birth. Congenital rubella is not a static disease; damage may continue. It is appropriate to recall that Gregg made the following observation in his first report: 'we cannot at this stage be sure that there are no other defects present which are not evident now but will show up as development proceeds' (Gregg 1941). The study of the natural history of congenital rubella is far from complete. One can cite, for example, the recent observations of Forrest *et al.* (1971) on the higher than expected incidence of diabetes mellitus.

In the preceding part of this paper, the spectrum of disease as it affects the individual subject has been discussed. The impact of intrauterine rubella on the community is also of importance, particularly in relationship to the recent preventive measures adopted. It has been estimated that approximately 20 000 affected infants were born after the epidemics in the United States in 1964–1965 and that the cost of the epidemics in economic terms was $920 000 000 (National Center for Disease Control 1969). Of course, this massive problem is not an annual event. The problem is far less significant in non-epidemic years. In the United Kingdom, for example, it is estimated that approximately 200 children are born with congenital rubella in a non-epidemic year (Dudgeon 1972). These cases will vary from severe multiply handicapped children to those with the more manageable handicap of deafness. The National Congenital Rubella Surveillance Programme was instituted at the time that rubella vaccination was introduced (1971) and in the first 12 months, 71 cases (25 with multiple defects and 46 with deafness) were identified by the Southern Registry, which serves approximately half the population of the country. These 71 cases represent about three-quarters of the estimated cases in half the total population. The determination of the annual incidence is an important aspect of the plans to prevent congenital rubella by immunizing the susceptible female population in this country.

The recognition and careful study of the clinical manifestations is the first step towards solving the question of the mechanisms by which damage occurs. These are by no means clear. They are undoubtedly multiple and depend on the tissue or organ infected, the time of infection, persistence of the virus, immunological reactions to the infection and possibly other factors, such as substances produced by rubella-infected foetal cells and damage to chromosomes. Understanding the mechanisms of damage is relevant, not only to this intrauterine infection, but perhaps to other foetal infections as well.