A Puzzling Respiratory Virus

Respiratory syncytial virus is the most important respiratory pathogen of early childhood. This is because it causes bronchiolitis and pneumonia[1-3] usually in infants less than 6 months old and especially in those aged 1-2 months.[4] This is surprising because infants of this age are usually protected by maternal antibody—and most babies do in fact possess maternal antibody against the respiratory syncytial virus. In older children and adults it is known that reinfection with this virus can take place despite the presence of neutralizing antibody.[5-8]

Thus respiratory syncytial virus is unusual among viruses in that neutralizing antibodies do not protect against it. Consequently the preparation of an effective vaccine against it might be thought difficult, but an even stranger situation was disclosed by the results of trials of inactivated virus vaccine in the U.S.A. Not only were vaccinated children not protected, but among them a higher proportion of those who later became infected with the virus developed pneumonia or bronchiolitis than did the children in comparable control groups.[9-11] Vaccination against the virus, therefore, both failed to produce immunity and actually increased the severity of the disease produced in those children who afterwards became naturally infected with it.

This unexpected result suggested that antibody produced in the serum by vaccination—or possibly also by previous infection or passive transfer from the mother—had in some way enhanced the severity of naturally acquired infection with the virus. A somewhat similar situation to this has been found with the vaccine made from inactivated measles virus, since a few of the children given this vaccine have developed an atypical, severe disease when they later became naturally infected with measles.[12,13] In the case of measles this complication has been attributed to delayed hypersensitivity.[14] But delayed hypersensitivity is almost certainly not responsible for lower respiratory tract disease in respiratory syncytial virus infection, because it is mediated by cells, which do not pass from mother to fetus. Chanock's team[4] has postulated that respiratory syncytial virus bronchiolitis and pneumonia, whether acquired as a natural infection in infancy or induced by vaccination, may be due to a type 3 or Arthus-type allergic reaction in the lungs.[15] In this type of reaction an acute immunological injury results from the formation of complexes between antibody and virus which are toxic to cells and thus give rise to tissue damage. Imbalance between the presence of serum antibody and the lack or relative lack of local IgA antibody in respiratory secretions was also suggested as a possible additional factor.

At page 327 of this issue of the *B.M.J.*, Dr. P. S. Gardner, Miss J. McQuillin, and Professor S. D. M. Court make some speculative observations on this interesting and important topic. They found that virus antigen was abundant in the lungs in one case of respiratory syncytial virus pneumonia but was scanty in two cases of bronchiolitis. Human globulin, on the other hand, was present, though sparsely, in bronchiolitis but could not be found in the lungs of the patient with pneumonia. If these observations are typical, they make it unlikely that either bronchiolitis or pneumonia are due to a type 3 reaction, since this would require the presence of excess virus antigen and antibody in the lungs, leading to the formation of antigen-antibody complexes.

The authors suggest that a type 1 or anaphylactic reaction[15] is a more likely explanation of the pathogenesis of bronchiolitis. In this type of reaction the cells of the lung would be sensitized by reagin, or IgE antibody, formed as a result of a primary encounter with the virus or by vaccination. The sensitized cells would then suffer immunological injury if virus antigen were later introduced again during reinfection. Since reagins are not passively transferred from mother to fetus, this explanation would mean that in the absence of vaccination infants with bronchiolitis—even those under 3 months of age—must have undergone an earlier infection with respiratory syncytial virus which resulted in sensitization. Though at first sight this seems unlikely, Dr. Gardner and his colleagues point out that infections with this virus are so common that infants of this age might have been twice infected with the virus.

Some indication that this may indeed be the case comes from the observations of H. W. Kim and her colleagues[16] that infants in the acute phase of respiratory syncytial virus infection of the lower respiratory tract had moderately high levels of neutralizing antibody, presumably largely IgA, in their nasal secretions. Dr. Gardner and his co-workers point out that this early nasal antibody may well have been the result of previous infection with the virus. They also suggest that the pathogenesis of respiratory syncytial virus pneumonia is different from that of bronchiolitis in that in pneumonia there is a widespread and primary virus infection of the lungs in the absence of IgA antibody.

Further work is necessary to see if the findings of the three cases described here are typical of most cases of respiratory syncytial virus bronchiolitis and pneumonia and also to investigate, perhaps by immunological as well as virological techniques, the pathogenesis of both diseases. The role of IgA antibodies in these diseases certainly requires further study.

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Compression of Coeliac Axis

The introduction of relatively safe techniques of aortography has focused increasing attention on segmental areas of narrowing or occlusion of the aorta's visceral branches, particularly since advances in vascular surgery now enable arterial reconstruction to be carried out. The clinical picture of intestinal angina, comprising abdominal pain after meals,

diarrhoea, intestinal malabsorption, and hence weight loss, is usually due to atherosclerosis at the origin of the superior mesenteric artery. In most cases there is also an associated obstruction at the origin of either the coeliac axis or the inferior mesenteric artery or both. Indeed at least two of these three branches must usually be narrowed before symptoms of intestinal angina become manifest. This is because of the excellent collateral circulation between them.

In 1965 J. D. Dunbar and his colleagues[1] described isolated stenosis of the coeliac trunk in 15 patients, mostly females, due to partial compression by the median arcuate ligament of the diaphragm. Division of this ligament in 13 of these patients resulted in relief of symptoms. T. Drapanas and K. M. Bron[2] considered that isolated stenosis of the coeliac artery, apart from its angiographic interest, rarely has any part in causing intestinal angina or other abdominal complaints if neither the superior mesenteric nor the inferior mesenteric artery is narrowed also. They studied 17 patients with isolated stenosis or occlusion of the coeliac artery found either incidentally during the investigation of some other condition or as a result of investigating abdominal angina. In six of these cases the coeliac artery stenosis was an incidental finding, and no symptoms of abdominal pain could be attributed to it. In six further patients other conditions were responsible for the abdominal symptoms—for example, carcinoma of the pancreas or chronic duodenal ulcer. Of the remaining five patients one was found at laparotomy to have almost identical pressure in the coeliac artery distal to the block as in the abdominal aorta. A shunt between splenic artery and aorta was performed, but the patient's abdominal symptoms continued. In the second patient adhesions which were kinking the coeliac artery were freed, but symptoms persisted despite the fact that a subsequent angiogram showed there was no longer any stenosis in the artery. Each of the remaining three patients had an extensive psychiatric history and a variety of symptoms. The high incidence of psychiatric illness in this group led these authors to doubt whether an attempt to correct the coeliac artery stenosis by surgical means would cure the symptoms, particularly if adequate collateral vessels from the superior mesenteric artery could be seen on the aortogram.

Apart from atheromatous narrowing of the coeliac trunk and nipping by the median arcuate ligament, other causes of coeliac occlusion have been described, including congenital stenosis,[3] fibromuscular hyperplasia,[4] adhesions, kinking, retroperitoneal fibrosis, and compression by adjacent ganglionic tissue. James P. Carey and colleagues,[5] reporting two cases, considered that relief of symptoms owed much to perivascular sympathectomy and denervation of the coeliac ganglion when freeing the coeliac artery from obstructing fibres of the diaphragm. They obtained some confirmatory evidence for this view from experiments on dogs.

In this issue of the *B.M.J.* (page 342) Mr. A. J. Edwards and his colleagues report a careful investigation of a small group of patients with the coeliac axis compression syndrome treated at St. Bartholomew's Hospital. They note that of 61 patients who have undergone surgical operation in five centres 59 have been followed up, and no fewer than 47 were rendered asymptomatic. The experience of Edwards and his colleagues was much less favourable, in that of five patients operated upon only two were improved despite the fact that direct measurement of blood flow at the time of operation showed that the obstruction had been abolished. The St. Bartholomew's investigators also found that epigastric bruits were present in 6·5% of 200 normal volunteers between the ages of 17 and 30 and there was no evidence that the incidence of bruits was higher in young persons with dyspepsia than in those without. Evidently further careful and critical studies of the kind here reported are necessary before the coeliac axis compression syndrome can be fully evaluated.

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Vaccination against Rubella

Live attenuated rubella virus vaccines have already been licensed in a number of countries, including the U.S.A., Australia, South Africa, Belgium and Switzerland. The Department of Health and Social Security has now stated that such a vaccine, the Cendehill vaccine, is available for use in Great Britain. This development follows extensive trials with attenuated vaccines conducted during the last four years.[1-4]

The first vaccine to be developed (HPV 77) was prepared by serially passing rubella virus 77 times in cultures of vervet monkey cells.[5] The virus became attenuated but did not lose its antigenicity. Thereafter further vaccines were developed, attenuation being achieved by serial passage in primary rabbit kidney (the Cendehill vaccine[6]) and other cultures.[7-9]

About 15 to 20% of women of child-bearing age in urban communities have not had rubella and therefore may catch it. Most commonly infection is acquired from close exposure to an infected person, particularly to children. Though it is difficult to estimate the annual incidence of rubella-caused congenital deformities, it was estimated that the extensive rubella epidemic in the U.S.A. in 1963–4 resulted in the birth of between 10,000 and 20,000 infants with one or more congenital abnormalities.[10] In addition many conceptions ended in abortions and stillbirths. Though pregancy may be terminated if rubella is likely to damage the baby, some patients experience atypical or even inapparent infections which are unrecognized but may nevertheless result in congenital anomalies. In addition a recent long-term follow-up study suggests that, even if infection is acquired after the first 16 weeks of pregnancy, fetal damage may still occur, though the results are less pronounced than when rubella comes earlier in pregnancy.[11]

The results of numerous trials of different vaccines on many thousands of volunteers are broadly in agreement with one another. In general, over 90% of seronegative persons develop serum antibody, though titres are often 4- to 8-fold lower than those following natural infection. In addition, some vaccinated persons excrete virus intermittently, usually between 10 and 27 days after vaccination. The prospect of immunity being long-lasting is encouraging, since there is little apparent fall in antibody titre for periods up to three years after vaccination, but only long-term studies can determine whether antibody persists indefinitely, as it probably does after naturally acquired infection. This is of particular importance if it is eventually hoped to offer vaccine to children with a view to protecting them when they grow up and reach child-bearing years. These results appear promising.

Many studies have shown that attenuated rubella virus vaccines protect volunteers exposed artificially to non-attenuated virus or to natural infection.[12,13] But it was recently reported that 47% of children vaccinated subcutaneously with