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INFECTION IN THE NEWBORN BABY*

BY

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It is a great honour to give the Charles West Lecture, and I appreciate it all the more because this is the centenary year of the famous hospital he founded in Great Ormond Street. I am also happy that on the first occasion this lecture is given by a London paediatrician it has fallen to the lot of one who also had the privilege of serving the Middlesex Hospital, where West was a lecturer on midwifery in the years before he devoted his undivided attention to the sick child. I have chosen the subject of infection in the newborn baby partly because of West's own interest in this subject as an obstetrician and also because I believe it was through this subject, encountered when he was studying in Dublin, that he first became interested in the sick child.

Charles West's Activities

Previous lecturers have given short sketches of Charles West, but this year I beg leave to say a little more by way of introduction. He was a Fellow of this College, Senior Censor, and Harveian Orator. His Fellowship came the same year as he first published his famous book, *Lectures on the Diseases of Infancy and Childhood*, based upon lectures to the students of Middlesex Hospital during the summer of 1847. It is rather surprising that, although officially the lecturer in midwifery, West devoted comparatively little space in his book to diseases of the newborn baby. He writes of "atelektasis"—a form of spelling now discarded—and in recognizing a congenital form he stresses the considerable pressure sometimes required to inflate the lungs. He notes that facial palsy can occur in the newborn baby "from injury received during the passage of the head through the pelvis without any instruments having been employed." West mentions that recovery in a few weeks is the usual story. He also makes the observation in regard to icterus neonatorum that it seems to be common if the child is chilled.

It is, however, in West's comments on "trismus" that we find a clue to his subsequent activities. He uses this term for tetanus neonatorum, but, like Cameron (1929), he recognizes that trismus can be caused by sepsis and that it is not always due to tetanus. In writing of this condition he states that "sixty years ago"—that is, during the closing decades of the eighteenth century—every sixth child born in the Dublin Lying-In Hospital died within a fortnight, and trismus was the cause in 19 out of 20 cases. Efficient ventilating of the hospital was then achieved—so runs West's story—so that by 1833 the mortality had fallen from 1 in 6 to 1 in 58½, and only 1 in 9 were due to trismus.

The points to be noted here are the appalling mortality among newborn babies, much of which was due to infection, and the reduction of the risk by certain elementary hygienic precautions. The fear of infection among children in hospital was the dominant factor in deciding policy in the early part of the nineteenth century. West was clearly impressed by the seriousness of the problem as he saw it in the lying-in hospital and by the statistical evidence of improvement achieved by certain measures. First he became interested in the sick child, and next in the provision of properly conducted hospital facilities. Hence "Great Ormond Street"; and, as Cameron has put it, "it is to obstetricians that the study of paediatrics owes its birth."

Some Scottish Figures

Charles West gave statistics to illustrate the events in Dublin, which so greatly influenced his life. I must now interpolate some more modern figures to indicate the possible extent of the problem. For this purpose I propose to rely almost entirely on reports from Scotland, because it happens that there are a series of figures available over the last twenty years which illustrate the chief aspects of the subject. Cruickshank (1930), in his study of neonatal death, ascribed this to infective conditions in 238 out of the 800 infants examined *post mortem*. He classified about 15% of the 800 infants as suffering from septicaemia, but thought this approximate and likely to be too low. For the purpose of this lecture Cruickshank's report is important for two things. First, that at least 30% of babies dying in the first month of life were dying of infection; and, secondly, that in only 7 out of the whole 800 was he satisfied that the form of infection could be called "umbilical sepsis." He stresses that nowadays umbilical sepsis is a rare variety of neonatal infection and that local umbilical stump infection is also most unusual. This is an important negative point, for far too many people to-day, doctors and midwives, in my experience, associate the word sepsis when used in reference to the newborn as meaning only umbilical sepsis. It is well that a pathologist from the city where Lister worked should stress the rarity of umbilical sepsis in the post-Lister era.

A real step forward towards recognizing other forms of neonatal infection can be made when this fact is firmly recognized. Confusion perhaps exists because a mild superficial omphalitis is not uncommon after the cord has separated, and it is not unusual in welfare centre work for babies to have a slightly blood-stained discharge, with or without an "umbilical polyp," about the second fortnight of life. This very rarely causes

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more than local trouble, and has nothing in common with the devastating umbilical sepsis such as West undoubtedly saw in the lying-in wards a century ago. Cruickshank's figures are almost the same as those of Agnes Macgregor (1946), who, working in Edinburgh, found infection to be a cause of neonatal death in 190 out of 618 infants, or 30.7%. This was the commonest single cause of neonatal death. It was responsible for two out of every three deaths after the third day of life. Both the Glasgow and the Edinburgh figures refer essentially to the period before modern chemotherapy became available, and it is likely that the incidence of infection as a cause of death in the newborn is less to-day.

Sepsis must, however, be recognized if it is to be treated efficiently, and unfortunately there is evidence that the condition is often overlooked. A further report from Scotland makes this point clear (Department of Health for Scotland, 1947). Discussing in general terms the neonatal mortality in Scotland, the report notes "that in a considerable proportion of deaths the cause is erroneously certified." Figures given for the period 1939–43 at the Royal Maternity Hospital, Glasgow, show that in the first three days of life deaths due to infection proved *post mortem* accounted for 15.4% of the total deaths, whereas on the clinical diagnosis only 3.5% were recorded as due to infection. For the first week the figures were 20.5 and 8.5% respectively, and over the whole of the first month of life 36.4 and 17.6%. It is noteworthy that it is in the early days of life that the clinical diagnosis is more often erroneous. Figures from four municipal hospitals in the same city over the same period revealed a similar discrepancy. On the whole the figures in Scotland show lower figures for smaller hospitals and hospitals taking fewer emergency cases.

The Common Cold

What perhaps is most striking in the Scottish report is that it makes no mention of what is in my opinion a common cause of trouble just because it is so common—namely, the common cold. It is, of course, probable that when this kills, as it may quite often do in the newborn, and especially in the premature infant, it kills by bronchopneumonia or by gastro-enteritis. What seems clear is that it is often missed as a clinical entity. It is interesting to note that in another report covering the whole subject of neonatal mortality and morbidity (Ministry of Health, 1949) the section on infection in the newborn also fails to mention the common cold, and as one of those who helped to draw up this report I must clearly accept some responsibility for this omission.

Why is the common cold not recognized in the newborn? It is because the pattern of disease in infancy, to use Spence's (1941) term, is different from the pattern in adults and so variable as to give little direct help in diagnosis, which has largely to be on circumstantial evidence.

Consider the clinical features of a small baby with a cold. Lying horizontally in bed, he seldom sneezes, and such excess secretion as is present from the nasal mucous membrane passes down the back of the throat. Obstruction of the nose may occur from time to time, leading in the early days of life to breathing difficulties, often quite wrongly attributed to "asphyxia neonatorum." The obstruction also leads to great difficulty over feeding, because the infant cannot suck properly. The result of this may often be engorgement of the breasts in the mother and a failure of lactation—or the baby is weaned because he will not take the breast. The diagnosis of intracranial haemorrhage may be made at this point. Sometimes, but in my experience, rarely, some degree of snuffles and anterior nasal discharge occur, often leading to a suspicion of syphilis and delay while this is excluded. By now the infant may have begun to vomit or have green stools as a manifestation of his parenteral infection.

Alternatively, infection may have spread down the respiratory tract and signs of involvement of the finer bronchi and alveoli of the lungs appear. Whether or not the primary infection of the nose was a virus, there is by now secondary invasion—staphylococcal or by one of the Gram-negative group. All this may happen with surprising rapidity, and death may occur within a few days of the onset, again without any suspicion that the original infection was essentially of the upper respiratory tract. Again and again with this picture it is possible to track the infection back to the baby's contact with an adult who has a nasal infection. The mother herself may have a chronic sinus infection (as in one of my patients), or the trouble may have come from one of the nursing staff (in one instance a night nurse in a nursing-home where at that period the matron did not "hold" with masks). Things are perhaps a little better than they were, because the use of masks is more widespread, but so long as the cold is largely unrecognized in the baby for what it is the menace will continue.

Difficulties in Diagnosis of Infection

Two fundamental difficulties seem to exist in the failure to recognize neonatal infection for what it is. First, there is a popular tradition that babies do not "catch" infections. This is of course based upon the fact that the common infectious fevers are uncommon in the early months of life. This is presumably due to temporary passive immunity transferred from the mother across the placenta. It can occur only if the mother herself is immune. Hence although the infectious fevers are rare in early infancy they can all occur. I have myself seen chicken-pox at 3 weeks, and I have performed an emergency tracheotomy for laryngeal diphtheria at 10 weeks. I have knowledge of whooping-cough more or less from birth, the mother herself suffering from the disease at the time of birth; and the literature contains records of unusual cases of the other specific fevers, when the mother has no immunity to pass on. In the case of other infections—those caused by staphylococci, pneumococci, for example—or the common cold, maternal immunity is not likely to be very solid, and therefore the newborn baby is not protected against these common infections. I shall refer later to the larger question of transferred immunity; here it is sufficient to emphasize that the baby is unlikely to have immunity unless the mother possesses it, and that maternal immunity to the infections just mentioned is never permanent.

The second reason for difficulty in accepting a diagnosis of infection in the neonatal period is concerned with the temperature chart and what is meant by fever. All newborn babies, and more especially prematurely born infants, tend to have a basic temperature at first below the commonly accepted adult levels. Thus if 99° F. (37.2° C.) is accepted as an average rectal temperature reading in the adult (or older child), a corresponding figure for the early days of life is nearer 97° F. (36.1° C.) and sometimes lower. This slowly rises as the infant's metabolism and heat-regulating mechanism get adjusted to post-natal life, but the "adult" level is often not reached for 10 or 14 days. A rise of 2° F. (1.1° C.) during the period will still only bring the baby to the "adult" level. If the temperature of the baby has not been recorded until some unusual symptoms and signs appear it is quite easy, after a reading of say 99 to 99.5° F. (37.2 to 37.5° C.) has been recorded by a rectal thermometer, to assume that no "fever" is present, and hence infection is an unlikely explanation for the infant's malady. Yet in fact the rise in temperature is more nearly equivalent to a reading of 101° F. (38.3° C.) or more in the adult, and from the point of view of a rise in temperature is quite clearly fever in the usual sense of the word. These points are illustrated in Figs. 1 and 2, and I have added for the sake of completeness a chart (Fig. 3) to show how sometimes overwhelming infection in the newborn actually causes a subnormal temperature before death. Regular daily temperature-recording should be carried out for all babies (as for all mothers) in the newborn period, so that an early rise can be detected.

If these two fundamental difficulties are kept in mind the diagnosis of sepsis in the newborn becomes easier, but it still remains difficult. Spence (1941) makes a valuable generalization: "A newborn infant who becomes abnormally

drowsy and refuses its feeds and is not suffering from cerebral haemorrhage should be suspected of an acute neonatal infection." I would go a little further and state that *any* disturbance in the newborn baby after the first few days of life should be regarded as due to infection until proved otherwise. Let me here record a personal failure to observe this rule.

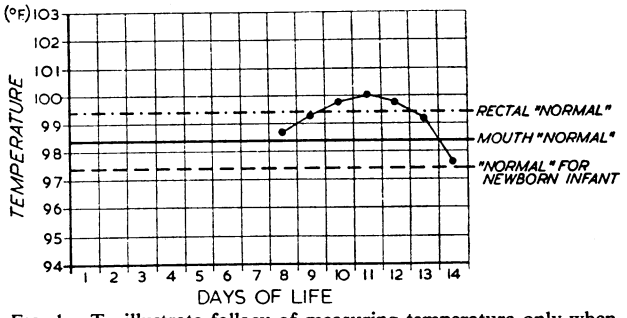

FIG. 1.—To illustrate fallacy of measuring temperature only when infant becomes ill—for example, on the eighth day. By "adult" or "normal" standards no rise is detectable and fever may be declared absent (cf. Fig. 2).

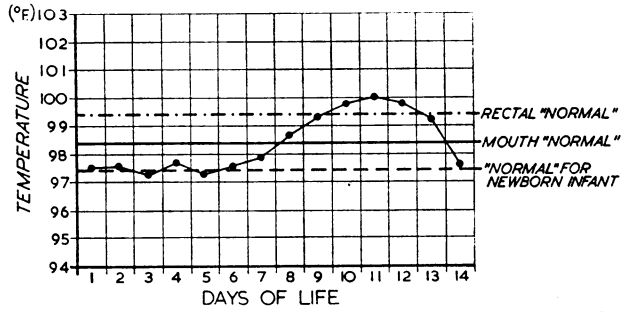

FIG. 2.—When temperature is measured daily from birth the rise on the eighth and successive days is clearly visible and there is no doubt about the febrile state.

A baby girl was admitted to my ward at the age of 5 days, having been seen by a colleague in a nursing-home. She was regarded as a case of haemorrhagic disease of the newborn, for on the third day she had begun to vomit small amounts of bright blood followed by brownish vomits for several days. There was a story that shortly after a normal labour she had regurgitated a little brownish mucus. Meconium had been normally passed. There was no melaena. The baby was not seriously ill. The rectal temperature on admission was 97° F. (36.1° C.). Clinical examination showed no signs of chest disease. The diagnosis of haemorrhagic disease was accepted and vitamin K was given for several days.' Four days after admission she had a cyanotic attack (subsequently it was learned that two slight similar attacks had occurred before admission). I carefully examined the chest but could find no physical signs. The child was taking feeds well, gaining weight (? due to oedema), and there was no further bleeding. At 10 days the child was vaguely not doing too well. White blood cells were 14,600 per c.mm., with 79% polymorphonuclears. There were still no signs. Then rapid deterioration set in. The temperature was still only 99° F. (37.2° C.) rectal—that is, 2° F. (1.1° C.) up—and for the first time there were signs in the chest: weaker air entry at the left base with crepitations. Puffiness of the face and distension of the abdomen developed. Aureomycin was started, but was much too late. The baby died next day. At necropsy there was a right-sided empyema and multiple lung abscesses suggestive of an inhalational septic pneumonia. *Staphylococcus aureus* (coagulase-positive) was grown from the empyema.

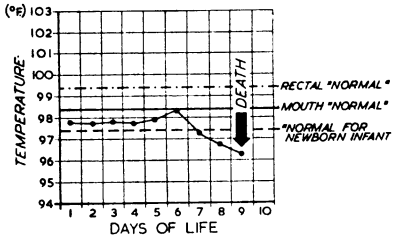

FIG. 3.—Effect of overwhelming infection producing paradoxical fall in temperature before death.

Here, then, was a fatal case of neonatal sepsis in which the essential diagnosis was missed despite all the resources of a modern hospital and the expert supervision of what have been termed "high priced" clinicians. It serves to emphasize the essential difficulties of the subject.

I now would like to turn to certain special types of infection in the newborn, and I shall use the classification of infection acquired before, during, and after birth.

Infections Acquired Before Birth

Of infections acquired before birth *congenital syphilis* is the best known and most studied, and, beyond stating categorically that it is a completely preventable disease if routine antenatal serological tests are conscientiously done and treatment is instituted, I will omit further reference. *Tuberculosis* may occur in a congenital form.

In the case of a baby born at full term and weighing 7 lb. (3.2 kg.) the young mother had developed a pleural effusion at the sixth month of pregnancy, and although this was not proved to be tuberculous at the time there was clear evidence three years later of healed lesions in her lungs. The placenta was said to be normal to the naked eye. The baby became ill on the fifth day of life and died at 1 month of age. Post-mortem examination (by Professor R. W. Scarff) showed advanced miliary tuberculosis with the most marked changes in the region of the portal fissure. The lungs and spleen were also invaded by miliary tuberculosis. There is little doubt that this was a transplacental transmission of tubercle bacilli. The point of interest is the mild nature of the mother's illness.

Infection by *Bact. coli* has been recorded many times. I have records of a baby dying in a nursing-home on the 10th day of life with what I can only call a fulminating pyelitis with *Bact. coli* in the urine—before the days of chemotherapy. The mother had suffered from pyelitis intermittently during pregnancy, with a flare-up in the puerperium. I also recall a patient described to me by Professor W. C. W. Nixon in whom meningitis due to *Bact. coli* caused death about the 4th day of life: the mother also had suffered from pyelitis during pregnancy. Pneumococci can also pass across the placental barrier. Cruickshank (1930) mentions the case of a mother who had pneumonia just before her delivery. The baby died on the 3rd day of life and was found to have advanced lobar pneumonia with grey hepatization.

Turning from bacterial infections, we reach some fascinating and speculative problems. *Congenital malaria* has been much debated by experts and is well discussed in a monograph by the late Professor A. Eckstein (1946). He and Nixon also described undoubted cases occurring in newborn babies in a hospital where malaria was not endemic (Eckstein and Nixon, 1946). Jones and Brown (1924) described the case of a mother who had been travelling on the Continent: her baby, born in England, developed malaria on the 16th day of life. I have no doubt, from reading much of the literature, that the disease can be transmitted from the mother. Experts disagree about whether or not the parasite can pass across an intact and healthy placenta, and suggest that this can happen only when accidental tears occur. Perhaps there is a similar mechanism to what happens in rhesus factor incompatibility when the first and sensitizing baby's blood mingles with the mother's at the time of separation of the placenta. Many problems are concerned with this question of malaria in early life. Does it cause death *in utero*? Would it be justifiable to carry out malaria prophylaxis during pregnancy? Is congenital malaria the cause of a high infant mortality rate in endemic areas? Is there in babies born of infected mothers a "latent" malaria, with symptoms which mimic meningitis, causing anaemia, digestive disorders, coma, and convulsions? My experiences in two brief visits to East Africa suggest that the whole problem requires very careful thought. Malarial infection in early life is valuable, so it is said, for producing "immunity" or "premunity" among the adult African population. The children's physician, perhaps short-sightedly, ventures to ask about the price paid in infant mortality.

Toxoplasmosis may be mentioned next, as the infecting organisms are also protozoa. There is no question here about the congenital form with a high mortality rate in early infancy and the development of symptoms in survivors within a few weeks of birth. Again the question of the placenta arises. Few studies have been made, but it is reported in one instance to have been abnormal in colour and appearance. There have been numerous papers on the whole subject in recent times, and the problems are well reviewed by Wyllie, Fisher, and Cathie (1950). This communication also refers to published cases on newborn babies of infection by the fungus *Torula histolytica*.

Virus Infections

Next we come to a large group of virus infections about which it is possible to mention only a few special points. (I am indebted to my colleagues Dr. Martin Bodian and Dr. J. A. Dudgeon for particular help in this section.) Here, as probably with many antenatal infections, foetal mortality is high, and when the infection occurs in the first trimester of pregnancy congenital malformations may result, as in the well-known rubella syndrome.

The effects on the unborn child of *variola* and of *vaccinia* in the mother have been reviewed by Lynch (1932), and MacArthur (1952) has recounted experiences in Lanarkshire following vaccination as a result of a smallpox outbreak. There appear to be dangers for the unborn babe, and, according to Lynch, little immunity is transmitted by vaccination. (This is not in accord with the findings of Marsden and Greenfield, 1934.)

Herpes in the mother may be associated with the early development of encephalitis after birth (Quilligan and Wilson, 1951; Wildi, 1951), and it is tempting to postulate intrauterine infection. Zuelzer and Stulberg (1952) have reported examples of herpes with hepatitis in newborn infants, and in one of these there was certainly the possibility of transplacental transmission of the virus.

Poliomyelitis in the mother may not necessarily infect the baby, although abortion may occur (Baker and Baker, 1947). There are many dramatic records of caesarean section in a dying mother or even after death resulting in a normal infant (Stokes, 1946; Simmons and Ellis, 1949). On the other hand, there are also records in which the infant had poliomyelitis at birth (Aycock and Ingalls, 1946).

A rare but fascinating virus infection is that described nowadays as "cytomegalic inclusion disease." This is particularly important because it can be mistaken for haemolytic disease of the newborn, and the jaundice which occurs raises points of interest in relation to virus infection and hepatitis (see below). Cappell and McFarlane (1947) reported giant cells with cytoplasmic and intranuclear inclusion bodies in the organs of two infants alleged to have died of haemolytic disease although there was no evidence of blood-group incompatibility. They concluded that the lesions were identical with those found in the salivary gland virus disease of rodents and monkeys. France (1951) has reviewed the clinical picture and pathological findings, and by the kindness of my colleagues Dr. G. Newns and Dr. M. Bodian I am able to report the case of a child who died with a clinical diagnosis of neonatal hepatitis and was found at necropsy to have suffered from cytomegalic inclusion disease.

The mother suffered from an attack of "influenza" at the fifth month of pregnancy. The child was very premature by weight—3¼ lb. (1.6 kg.)—and on the second day of life showed slight jaundice which lasted only for 24 hours. Subsequently he developed pitting oedema of feet, legs, and abdomen, and when the oedema subsided at the age of 26 days the jaundice again became apparent. The stools contained bilirubin on two occasions. He made no real progress and developed a staphylococcal upper and lower respiratory infection, dying at the age of 11 weeks.

At necropsy there was pulmonary emphysema and collapse. The liver was slightly enlarged and olive-green, and the bile ducts were normal and patent. Histological examination showed the replacement of portal areas in the liver by granulation tissue and the almost complete disappearance of bile-duct epithelium. There was a retention of bile in canaliculi and hepatic cells, and many of the liver cells, principally in the peripheral parts of the lobule, were larger than normal, and some were multinucleate. The most interesting findings were in the submaxillary glands, which contained numerous intranuclear and intracytoplasmic inclusions in the epithelium of smaller ducts. A few scattered foci of cytoplasmic inclusions were also found in the convoluted tubules of the kidneys.

It is therefore concluded that this child suffered from cytomegalic inclusion disease which seemed to have affected epithelial cells in various situations, and it is suggested that the disappearance of the biliary epithelium was the result of this disease, although no inclusions were, in fact, found in the bile ducts or in the liver cells. This would appear to have been a case of hepatitis and cholangitis due to cytomegalic inclusion disease.

Hepatitis

It seems likely from the early development of signs and symptoms that the "salivary gland virus" is transmitted from the mother. This also seems possible with the viruses concerned with hepatitis. Here we reach a complicated and very important subject. First let me describe some clinical problems in this field.

A trained nurse "caught" what was called infective hepatitis, presumably the "epidemic virus" type, in 1944. She had a moderate attack and recovered completely. She married, and in 1949 gave birth to a baby boy who was quite severely jaundiced for some time after birth but eventually recovered, although left with an enlarged firm liver which is almost certainly cirrhotic. Two years after the birth of the first child another boy was born who also became jaundiced, and died. Necropsy showed a classical picture of hepatitis.

Is there any connexion between the mother's jaundice and the children's condition? Could she have the virus still latent in the blood? It is held that the virus of epidemic jaundice is in the blood only at the time of the illness, and therefore unless the mother had the disease at the end of the pregnancy the baby would not be likely to be affected. Here is another case record:

A fifth baby was born at term to a rather feckless mother who was known to have had a positive Wassermann reaction and a positive Kahn reaction during pregnancy. The mother had an injection of penicillin at the sixth month and two more during the eighth month of pregnancy, and then defaulted. She had never been jaundiced, nor had any of the other four children. The baby had had no injections. (Incidentally, there never was any serological, clinical, or pathological evidence of syphilitic infection in the baby.) On the fourth day slight jaundice was seen which faded, and the stools were said to be pale. On the tenth day of life the jaundice deepened, the stools were usually pale, and the urine contained bile. The jaundice deepened further and the liver enlarged. Forty-eight days after this baby's admission the nurse who had been mainly responsible for his care developed what appeared to be a classical attack of infective hepatitis, and 16 days later—that is, 64 days after the first contact—a second nurse who had helped with the baby also developed jaundice. Both the nurses recovered after a mild attack. There had been no cases of infective hepatitis among the nurses for about a year and no more cases until six months after this curious episode. Unfortunately the story does not end here. Laparotomy undertaken to eliminate the possibility of obstruction of the bile ducts revealed an enlarged liver which showed in a biopsy the appearances of a biliary cirrhosis secondary to obstruction. The bile ducts and the gall-bladder could not be traced. The baby lived for several months and then died. At necropsy a blind end was found for the hepatic duct and no common duct. The histological appearances were not those of hepatitis.

It is still possible here that some infection from the mother played a part. In a discussion on this subject in the U.S.A. (Stokes *et al.*, 1951) the clinical resemblance between hepatitis in the newborn and atresia of the bile passages was stressed, and it was also mentioned that the histology was confusing. I am not suggesting that in the present case an error has been made: the anatomical findings leave no doubt about the atresia. It is possible, however, for hepatitis to be followed by fibrous-tissue repair sufficiently marked to cause confusion with the appearances in biliary cirrhosis due to obstruction.

A baby was admitted at the age of 5 weeks for jaundice which had started between the second and fifth days of life. The stools

became pale and the urine darkened. For various reasons the condition was regarded as hepatitis. The jaundice continued and the liver enlarged and became firm. Laparotomy revealed the absence of a gall-bladder or bile ducts. Some fibrous tissue lying round the hepatic artery was thought possibly to represent the remains of bile ducts. A portion of liver taken for biopsy showed, however, the picture of active hepato-cellular necrosis and post-necrotic regeneration together with reactive portal fibrosis. The picture was, according to Dr. Bodian, most complex and certainly not that found usually in atresia of the bile ducts.

These cases are of importance when it is remembered that to-day most pregnant women in this country have at least one needle inserted into a vein during the antenatal period, and the opportunity for the introduction of the virus of "serum hepatitis" is there. There is evidence that virus can cross the placenta. In the American discussion mentioned above (Stokes *et al.*, 1951) it was suggested that perhaps yet a third virus was involved and not that of serum hepatitis or of epidemic hepatitis. There was doubt, however, that hepatitis of viral origin can occur in the newborn.

Inhalation of Infected Material

So far the intrauterine infections mentioned have all been blood-borne to the foetus. There is also the possibility of inhalation of infected material.

In the early days of my work in the department for the newborn at the British Postgraduate Hospital the late Professor E. H. Kettle called my attention to a post-mortem examination of a stillborn full-time baby with changes in the left lower lobe very similar to those of pulmonary fibrosis in later childhood, of the type that often proceeds to bronchiectasis. He suggested that the changes were the result of an acute inflammatory process which had occurred three to four months before birth. Examination of the mother's records showed that she had been kept in bed for a few weeks just at this period for a uterine haemorrhage. It is tempting to suggest that partial separation of the placenta had been responsible for initiating inspiratory efforts on the part of the baby.

A recent study by White (1952) of 360 infants, either stillborn or dying during the neonatal period, included 69 infants (29 stillborn) who had aspirated appreciable quantities of particulate amniotic debris, and 39 other infants who showed formation of "hyaline membrane." Associated pneumonia was present in 29 and 12 infants respectively in these two groups. The evidence seems clear that the agent responsible is aspirated with the amniotic contents, possibly breakdown tissue products, the result of premature devitalization of parts of the placenta and foetal membranes. I have always felt that blood may be an irritant in the lungs provoking an inflammatory response, as it does, for example, in the peritoneal cavity in later life. Dr. White also found in a minority of cases of the severest degree, usually associated with prolonged rupture of the membranes, that bacteria could be demonstrated.

Infections Acquired During Birth

Infection during birth is so well recognized that it can be briefly dismissed. Inhalation again plays an important part. It is essential in the management of the newborn baby to carry out a gentle toilet of the mouth and nasopharynx, if possible before the first breath. Infection of the eye at the time of birth is illustrated by gonococcal ophthalmia, and although this has become rare in this country and is now so easily treated that many centres have given up the prophylactic use of silver preparations, the problem of the "sticky eye" still remains numerically one of the most troublesome in the neonatal period. Just as gonococcal ophthalmia has been known to lead to generalized infection on rare occasions, as shown by the development of a gonococcal arthritis, so ophthalmia due to other organisms is important not because of the mild and easily treated local condition, but because the eye may be a portal of entry for generalized "sepsis neonatorum."

It must also be remembered that during or immediately after birth the baby may meet for the first time infective material from other sources than his mother. The historical example of the tuberculous midwife who fatally infected several babies by mouth-to-mouth insufflation is scarcely likely to be repeated to-day, but streptococcal, staphylococcal, and virus infections still lurk in the upper respiratory tract of those attending the newborn, and great personal care is necessary to prevent infection at a period when immunity to such infections is low.

Infections Acquired After Birth

Any discussion of infection after birth ought to deal with the whole problem of immunity, but fortunately it has been well reviewed in recent times by several workers, and especially by Parish (1951). I shall select only a few aspects of the subject for comment.

Passive immunity in humans is probably transmitted almost entirely by the placental route, and certainly not by colostrum, as in certain animals (sheep, goats, cows, horses, and pigs). This species difference is important because it largely rules out arguments from veterinary experience so well reviewed by Lovell (1951). According to this doctrine, in the human subject transferred immunity depends on the layers of placental tissue and on placental permeability. Experiments by Bramball and others, quoted by Parish, throw just a slight doubt on this, however, because it is suggested that antibodies may be present in the amniotic fluid and be swallowed. If it is accepted, however, that the placental route is the more important, there at once arise problems of the size and nature of antibody particulates, whether the process is one of simple filtration or of active secretion or whether, as suggested by Calman and Murray (1951) in a fascinating hypothesis, the mechanism is one of selective passage. They suggest that antibodies in the foetal circulation may result from a breakdown of a complex molecule on the maternal side and the re-forming of antibodies on the foetal side. It is noteworthy that the blood of the foetus may actually have a higher measurable antitoxin level than the blood of the mother. This has also been shown to be true in relation to gamma globulin—for example, by Martin-Du Pan and Moore (1948)—a substance which many regard as the raw material, so to speak, of antibody function.

As regards the development of active immunity, we still do not know in detail how quickly newborn babies can respond by antibody formation when subjected to antigenic stimulation. It may be related to nutritional factors. Calman and Murray make this point when they refer to the amino-acid groupings provided by the mother for antibody formation. It has long been accepted that well-nourished people are better able to withstand infection. Actually experiments have shown that the relationship between nutrition and antibody formation is less close than tradition suggests. Well-nourished soldiers give only slightly better antibody response than others. It is generally felt that interference with amino-acid metabolism is probably more important than any general reduction in diet protein. Pyridoxine deficiency interferes with amino-acid metabolism, and experiments support the idea that antibody response is less in pyridoxine-deficient rats (*Lancet*, 1950). The practical bearing of this lies in the question of whether anything can be done by diet to increase the immunity of the newborn. Is there any special amino-acid grouping which will help? Is there any value, from the immunity standpoint, in enriching human milk with casein hydrolysates in the early weeks for prematurely born infants?

Yet another aspect of neonatal immunity is that of genetics. Here again there is a lack of detailed knowledge.

Recently I had under my care a baby admitted at the age of 5 weeks for neonatal sepsis. This had begun with a stye in the right eye, a septic spot on the right cheek, and a septic thumb while in a nursing-home where he was born. At the age of 4 weeks an infected area appeared on the right leg, and the day before admission his right ear began to discharge. The rest of his life up to the age of 3 months was a losing battle against infection. Despite the use of every modern aid the child never seemed able to overcome the various organisms which invaded him. His cord did not separate until he was a month old, and he had some infection of a persistent urachal sinus. At necropsy the bony parts of his right ear were almost completely destroyed.

An elder child also died from chronic sepsis beginning at the age of 14 days with recurrent boils and cutaneous ulcers. He lived for 15 months, and the comment of a colleague under whose care he was for the last period of his life was that although "there was a good response by the reticulo-endothelial system" this was "not enough to eradicate the infection, even with the help of chemotherapy and fresh blood."

In the case of the second child the white-cell response was adequate throughout, and his response to inoculation with T.A.B. vaccine (to test his antibody response mechanism) was described by Dr. J. C. McFarlane, who kindly did the agglutinations, as "excellent."

Is this family an example of lack of immunity to bacterial invasion genetically determined?

Main Features of Infection After Birth

Coming now to the general picture of infection after birth, I will give a brief description of the main features. First, infection has to gain an entry by way of the mucous membranes of the respiratory tract, the eyes, the skin, the alimentary tract, or the umbilicus. Usually there is some local reaction which may be termed the "primary focus." If the infection is mild and resistance good nothing more may happen except that spread from one infected baby to another may take place—and a favourable outcome in one baby is not necessarily followed in other babies infected from the first. In unfavourable cases generalization of the infection takes place—either a toxaemia or a septicaemia at first, later frequently becoming a pyaemia.

Epidemic diarrhoea of the newborn requires a short separate note. It is fortunately rare, although a constant threat in newborn baby nurseries. It may be of virus origin (Buddingh and Dodd, 1944) or be due to a special serological type of *Bact. coli* (Kirby, Hall, and Coackley, 1950). It behaves like infective gastro-enteritis in older children. The picture of primary focus, generalization, and secondary pyaemia is overshadowed by the dehydration and metabolic disturbances.

The usual secondary stage of generalization produces the most difficult clinical picture, especially if the primary focus has been slight or has been missed. I have already dealt with this to some extent in discussing problems of diagnosis. Fever, as I have already explained, may not be obvious. The gain in weight ceases, the child refuses to suck and easily tires, vomiting and diarrhoea may take place, the pulse and respirations become rapid and irregular, and there develops an ominous grey look about the child, who becomes dehydrated and inert. Oedema of the legs is often present at this stage, and this retention of fluid may mask the weight loss. Jaundice is common and may fluctuate. Blood examination shows an anaemia. Blood culture may reveal pathogenic organisms. This is the picture of what is described as sepsis neonatorum: it should never occur.

The tertiary phase is essentially pyaemic. Skin abscesses or pemphigus, or abscesses in the liver, kidney, lungs, or bones, may develop, adding to the difficulties of diagnosis. This picture may occur with almost any organism. A gonococcal ophthalmia may end with a gonococcal arthritis. Thrush in the mouth may kill by a toxaemia. The common cold, presumably of virus origin with secondary staphylococcal invasion, may lead to generalized skin sepsis. A septic circumcision wound may end with pyaemic lung abscesses. A septic vaccination may end with pyaemic abscesses in the liver. These are all examples within my own experience. There seems every justification for a conclusion reached earlier that *any* disturbance after the first few days of life should be regarded as due to infection until proved otherwise.

Prevention and Treatment

This is the essential principle of *diagnosis*, and I shall say no more about this aspect of the matter. Clearly diagnosis must precede *treatment* and if possible should include identification of the infecting micro-organisms when this is possible. This will put the use of chemotherapy and antibiotics on a rational basis. Breast-feeding must be continued whenever possible. Dehydration must be dealt with on the usual lines. The haemoglobin level must be watched. As a working rule, if this falls below 50% Haldane a blood transfusion is essential to enable the baby to overcome the infection. Local treatment must be utilized according to circumstances.

This is a very brief summary of what may be a complicated and prolonged campaign of treatment. More important is the *prevention* of infection, and in conclusion I will pick out some points for consideration in this field. On general lines the importance of the personal factor in the care of the newborn is great, as in all fields of the prevention of cross-infection. A high standard of personal hygiene must be scrupulously observed by all concerned. Adequate staff, well trained in the methods of infant care, can achieve a great deal. Figures given a year ago (Watkins, 1951) showed a reduction of a neonatal death rate from 43 per 1,000 to 24 per 1,000 in a maternity hospital in five years, during which time improved methods of care had been introduced. The use of efficient masks by the nurses and visiting staff is, I think, still important, although there is a tendency to decry their value. I do not think mothers need wear them if their babies are full-term, provided that they have no obvious upper respiratory tract infection. Visiting should be restricted to fathers, and when seeing the babies they should wear masks. Among other measures which have received attention in recent years I favour the aspiration of the gastric contents in premature babies as a routine measure in the first day or so after birth to prevent inspired material causing pneumonia. As regards care of the skin, I am still an unrepentant believer in the value of soap and water as a cleansing agent, sparingly used, followed by gentle drying with hot towels and the use of an absorbent dusting powder to mop up any remaining damp.

In a more speculative field I suggest that much might be done to raise immunity to staphylococcal infections in the newborn by the use of vaccines in the mother in the later months of pregnancy (Murray, Calman, and Lepine, 1950). This should certainly be investigated further, especially where penicillin-resistant strains of this organism are increasing. There is also a case for the energetic use of antibiotics and chemotherapy in the mother in cases of premature rupture of the membranes and prolonged labour, in the hope of preventing infection in the baby. As already suggested, there may be some association between nutritional factors and resistance to infection. More work is needed on this subject. The value of adding amino-acids to the diet of premature babies, for example, may lie more in the field of immunity than in merely provoking a better gain in weight.

There is certainly scope for research in the prevention of infection in the newborn, and it should be a profitable field, for babies saved will be unlikely to have the permanent damage which afflicts some of those treated for other neonatal maladies, such as rhesus incompatibility or cerebral trauma or respiratory failure.

My sincere thanks are due to many colleagues who have helped in the preparation of this lecture, and to them and others I am also deeply grateful for continued assistance and encouragement over many years at the various hospitals where I have been permitted to work with the newborn babies. I also owe a debt to the midwives and nursing staff, whose co-operation has been always so willing.

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AN EPIDEMIC OF INFLUENZA DUE TO VIRUS B

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A city may not be the ideal place for the conduct of precise epidemiological investigations; both its size and the complexity of its intercommunications make the course of events difficult to trace with accuracy. Nevertheless, the continued study of such epidemics is obviously essential not only because of their magnitude but also for the simple reason that most epidemics occur in cities. A large epidemic of virus B influenza in the city of Glasgow seemed a sufficiently unusual event to make it desirable to study, so far as possible, the natural behaviour of the infection in this large community. The Public Health Department of the city has, over a long period of time, paid considerable attention to the study of respiratory infection, so that it is possible to utilize statistics which might not be generally available.

Indicators of the Occurrence of an Epidemic

Accurate figures regarding the incidence of influenza are not obtainable. That infections due to influenza virus B had appeared in the city was proved by the demonstration of a rising titre of antibody in the paired sera from two cases of pneumonia which were examined on February 25, 1952. The histories obtained from these patients suggested that the earliest date of sickening was February 8, 1952. Subsequently, with the assistance of the Virus Reference Laboratory at Colindale, virus B was isolated from a fatal case of fulminating staphylococcal pneumonia. It is not intended in this report to analyse the results of the serological studies. It is sufficient to state that these, as well as other related epidemiological investigations, show beyond doubt that there was a high prevalence of virus B infection in the city during late February and March, 1952.

Some idea of the course of the epidemic can be obtained from the accumulated statistics of (*a*) the weekly new claims to the Ministry of National Insurance; (*b*) the weekly notifications of pneumonia; and (*c*) the weekly deaths from respiratory disease. These figures are supplied in Table I for the period December 1, 1951, to March 31, 1952.

(*a*) *New Claims to the Ministry of National Insurance.*—Study of these figures shows that the whole period can be divided roughly into three: the last weeks of 1951 and first week in 1952 constitute the first interval, when the figures were low; the 2nd to 8th weeks a second interval, when the figures had increased by about 50%; during the 9th to 13th weeks a further increase was noted, which reached a peak in the 10th and 11th weeks, falling in the 13th week to the pre-existing level. If the figure for the first week of the study period is regarded as 100%, then at the peak the new claims had increased to about 250%. The first interval, of course, includes the Christmas and New Year weeks, when a drop in the reporting of minor illness is a usual occurrence. When this is appreciated, the figures suggest that during the early weeks of 1952 there was a gradual increase in sickness, which culminated in the more accentuated rise in the 8th to 12th weeks.

(*b*) *Notifications of Acute Primary and Influenzal Pneumonia.*—The figures of notifications of pneumonia in Glasgow are more valuable than in many other cities. Since 1925 the practitioners have been encouraged to notify their cases, a large proportion of which are admitted to the infectious diseases hospitals. The notifications showed a rather steady increase from the first week of the study period. In the 7th week of 1952, however, a much more rapid rise began, which reached a peak in the 9th week, to return in the 13th week to a figure similar to that encountered in the earlier interval.

TABLE I.—*(a) New Claims to the Ministry of National Insurance, (b) Notifications of Acute Primary and Influenzal Pneumonia, (c) Deaths Registered from Respiratory Diseases (excluding tuberculosis); December 1, 1951, to March 31, 1952*

Week	(a)	(b)	(c)
49	3,957 (100)*	63 (100)	14 (100)
50	3,840 (97)	85 (135)	23 (164)
51	3,647 (92)	111 (176)	32 (223)
52	2,537 (39)	117 (186)	29 (207)
1	2,991 (50)	99 (157)	21 (150)
2	4,576 (116)	148 (235)	29 (207)
3	5,604 (142)	119 (189)	21 (150)
4	4,809 (122)	158 (251)	45 (321)
5	5,640 (143)	174 (277)	56 (400)
6	6,265 (159)	181 (288)	67 (478)
7	5,525 (140)	220 (350)	43 (307)
8	6,003 (152)	231 (367)	53 (378)
9	7,847 (199)	368 (585)	75 (536)
10	9,772 (247)	336 (534)	84 (600)
11	9,697 (245)	268 (426)	84 (600)
12	6,886 (147)	193 (307)	53 (378)
13	4,974 (126)	117 (186)	40 (286)
Totals ..	94,570	2,988	769

*The figures in parentheses are percentages of the figure for week 49.

The peak of notifications was reached in the week preceding the peak of new claims to the Ministry of National Insurance. At first sight this seems surprising, but it is possible that, as information of the presence of an epidemic becomes publicized, there is a greater tendency for the individual to pay attention to minor illness and to remain off work.

(*c*) *Deaths from Respiratory Diseases, Excluding Tuberculosis.*—Here, after a fairly steady number during the beginning of the period, an initial rise is noted in the 4th week, followed by a moderate increase in the 9th, 10th, and 11th weeks.

These figures combine to indicate that during the latter part of February and the first part of March, 1952,