The Use of Penicillins in Neonatal and Paediatric Practice

J. P. M. Tizard, BM, FRCP, Professor of Paediatrics, Institute of Child Health and Royal Postgraduate Medical School, Hammersmith Hospital, London

In the past thirty years there has been an astonishing decline in infant and childhood mortality, which it is natural to attribute in large measure to the introduction of penicillin and to the therapeutic developments that have flowed from this great discovery. However, the decline in childhood mortality rates between the 1930s and 1960s may misleadingly exaggerate the importance of antibiotic and chemotherapy, as a critical analysis of mortality statistics over a longer period suggests.

Figure 1 shows the infant mortality rates per thousand live births from 1900 until the present day, the arrows indicating the years in which penicillin became freely available in hospitals and when it could be prescribed in general practice. Figure 2 shows, for the same period, the mortality rates per thousand living for the ages 1 to 5 years, 5 to 10 years and 10 to 15 years.

An uncritical glance at these graphs might suggest that the introduction of penicillin had little effect in speeding the already rapid decline in mortality rates but this would be equally misleading.

When disease due to a multiplicity of factors is declining because of improvements in social conditions, nutrition, and medical treatment, one would expect the secular mortality rates for the young to describe a sigmoid curve. Figures 3 and 4 show a logarithmic transformation of the statistics in Figs 1 and 2 where the curve appears to be exponential. Figure 3 shows the infant mortality rate as describing an almost straight line; however, Fig. 4, which shows the mortality rates for children from the 5 to 10 year age group suggests that the antibiotic era has accelerated declining mortality rates. Nevertheless, Fig. 5, which shows the mortality rates for scarlet fever in children under 15 years old indicates that it might be fallacious to attribute an improvement in mortality rates to medical advances rather than to improving social conditions or declining bacterial virulence.

If the decline in mortality in childhood attributable to penicillin is not as easy to demonstrate as is sometimes thought, there are certain diseases, once almost always fatal, such as pneumococcal meningitis and subacute infective
endocarditis, that are not usually fatal today. Moreover, there has been a change in childhood morbidity so obvious as to need no statistical confirmation.

Professors Garrod and O'Grady (1971) have recently written: 'No one recently qualified, even with the liveliest imagination, can picture the ravages of bacterial infection which continued until little more than thirty years ago.'

What were then common distressing conditions in a paediatric ward are now rare, particularly suppurative conditions such as mastoiditis, empyema thoracis, bronchiectasis, and osteomyelitis with discharging sinuses. Another benefit to children from the introduction of the penicillins, used prophylactically, has been the reduction in the incidence of certain chronic and debilitating diseases; for example, bronchiectasis, and rheumatic heart disease, which is still a very common condition in underdeveloped countries. The use of the penicillins, whether for the treatment of acute diseases or for long-term prophylaxis, has been attended by remarkably few ill effects. Sensitisation

Fig. 1. Infant mortality rates from 1900 (England and Wales).
reactions are unusual in children, and direct toxic effects of naturally occurring penicillin are even more unusual, apart from those caused by very high levels in cerebrospinal fluid. Penicillins do not normally cross the blood brain barrier well but in meningitis this is not so, and high levels of antibiotics may be achieved in the cerebrospinal fluid, through inflamed meninges. Because of relatively poor renal function in newborn babies the dose of penicillin must be scaled down, although it is sometimes difficult to judge
Fig. 3. Infant mortality rates from 1900 (England and Wales).

Fig. 4. Mortality rate (ages 5 to 10 years) from 1900 (England and Wales).
the correct dose. Failure of excretion causes abnormally high blood levels, and convulsions may occur if the dose is too large.

The most serious adverse effect seemed at one time to be the emergence of penicillin-resistant strains of staphylococci, mainly \textit{Staph. aureus}. However, at Hammersmith Hospital cross infection with penicillin-resistant staphylococci has ceased, at least temporarily, to be a serious problem in paediatrics. The initial improvement occurred with the antibiotic policy established by Professor Mary Barber, and the introduction of the semi-synthetic penicillins resistant to penicillinase has undoubtedly helped. Also of great importance in preventing the colonisation of the newborn with \textit{Staphylococcus aureus} have been the measures taken to stop the umbilical cord stump from providing a culture medium that permits the growth of staphylococci and their spread.

Fig. 5. Scarlet fever mortality rates from 1900 (England and Wales) ages under 15.
to other parts of the baby's body and even to the mother's breasts. Serious cross infection in newborn babies delivered in hospital today is mainly due to Gram-negative bacilli, especially *Pseudomonas aeruginosa*, but this is not as great a problem as was infection by *Staph. aureus*. Gram-negative septicaemia occurs mainly in very ill newborn babies, especially those nursed in incubators or treated with artificial ventilation or even remotely in contact with equipment that cannot be kept dry enough to inhibit the growth of the organisms.

Carbenicillin is usually effective in pseudomonas infections, but the emergence of resistant strains indicates that rather than relying on curing established infections, efforts should be made to prevent colonisation. We therefore use antibiotics as little as possible in sick newborn babies and have never given them for routine prophylaxis. We have no reason to regret this policy. For other reasons we are reluctant to use new antibiotics on newborn, particularly prematurely born, babies. The hepatic and renal immaturity of the newborn is such that unexpectedly high blood levels may be achieved and rapidly growing tissues may be damaged, though less by the penicillins than by other antibiotics. Although the cephalosporins are available for use in children who are penicillin sensitive or infected with penicillin-resistant organisms, we have not had much experience of their use in paediatrics.

It is interesting to speculate on the extent to which the use of the penicillins has been responsible for the recognition of a number of inborn errors of metabolism in childhood, the existence of which was previously not known or, if known, ill understood, since the victims did not live long enough to permit a study of their disorders. The most obvious of these are the immunological deficiencies, disorders of leucocyte production and function, and disorders of humoral and cellular immunity. In many of these conditions the child is beset with serious pyogenic infections, which respond at least temporarily to antibiotic treatment, but which were presumably quickly fatal before the introduction of antibiotics. Congenital agranulocytosis was first described by Kostmann in 1956, and agammaglobulinaemia by Bruton in 1952, although the recognition of the latter disease depended on the recently developed electrophoresis as well as on the survival of the affected children. To these must be added other conditions in which the impaired resistance to infection is of a different nature; for instance, cystic fibrosis, in which chronic pulmonary infections result from abnormal mucus secretion and ciliary function. There are also many other metabolic diseases in which death from infection used to occur early but in which the precise nature of the poor host resistance is still unknown.

Thus, the introduction of penicillin has had two unexpected results. First, it has enabled us to advance our knowledge of natural resistance to
disease by enabling us to study children with specific disorders of immunity. Secondly, children with certain inherited inborn errors of metabolism are surviving to parenthood. Two recent studies have shown the vastly improved expectation of life. Carter (1958) reported on the declining mortality of mongol children. These children may die in early life of congenital heart disease, intestinal obstruction, or leukaemia, but at the time of his study more than half of the early childhood deaths were due to infections, usually bronchopneumonia, and 50 per cent of the children were surviving to the age of ten years. In 1949 the survival rate was 25 per cent and in 1929 12 per cent.

A recent study of life expectation in children with cystic fibrosis (George and Norman, 1971) has shown that well over half the children now born with cystic fibrosis will be alive at 15 years of age compared with 10 per cent in the period 1943–64. The main cause of death in this disease is chronic pulmonary infection; the improvement in the rate of survival was initially due to penicillin; today treatment with the semisynthetic penicillinase-resistant penicillins is responsible for further improvement. Cystic fibrosis is an inherited autosomal recessive disease and is a common condition, about one in twenty being heterozygotes. Fresh mutations can adequately account for the persistence of rare and serious autosomal recessive disease, but the persistence of a common and serious autosomal recessive disease can be attributed only to an enhanced biological fitness in the heterozygote. One wonders what the future may bring.

The fear that modern medicine, including the use of antibiotics, will produce a race of cripples is a dismal prophecy; the fact that the penicillins have eliminated many forms of crippling disease more than offsets theoretical concerns about the future of mankind.

Doctors are often unfairly criticised for the misuse of antibiotics and other drugs; nevertheless misuse occurs. Sir Francis Galton wrote in 1872: ‘The traveller who is sick away from help, may console himself with the proverb, that “though there is a great difference between a good physician and a bad one, there is very little between a good one and none at all!” ’ The introduction of antibiotics, like that of other modern drugs, has perhaps widened the difference between a good physician and a bad one and may have created situations in which there is some difference between a good one and none at all.

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