Penicillin Treatment in Obstetrics and Gynaecology

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Almost all the serious infections that now occur in Queen Charlotte's Maternity Hospital and the Chelsea Hospital for Women are susceptible to treatment with penicillin or a related compound, usually ampicillin or cloxacillin. The indications for prophylaxis within this branch of medicine are few. Urinary tract infections are common, and endocarditis, neonatal meningitis and pneumonia occasionally occur. Gonococcal ophthalmia is treated as it arises, but venereal disease is treated in a special unit.

There remains a group of infections of similar aetiology that were once the scourge of obstetrics, and, to some extent, of gynaecological surgery; all are infections of wounds or of devitalised tissues. Puerperal sepsis, wound sepsis, and peritonitis following surgery are the rump of that hospital gangrene which formerly decimated in-patient populations. They are still of primary importance in obstetrics and gynaecology because of the high mortality of some, for example, post-abortal gas gangrene; and because of the fulminating course that may be run by streptococcal infections, where the interval between the eliciting or reporting of the first sign or symptom and the patient's death may be as little as six hours. Most important of puerperal and of other wound infections are those caused by β-haemolytic streptococci of Lancefield's Group A because they can occur in epidemic and in fatal form.

The final elucidation of the pathogenesis of streptococcal puerperal sepsis, of its relationship to sore throat or to scarlet fever, and of the route of transmission of haemolytic streptococci to parturient women was the work of Leonard Colebrook and his colleagues at Queen Charlotte's Hospital and elsewhere. Colebrook demonstrated the efficacy of prontosil (Colebrook and Kenny, 1936) and, later, of sulphonamide (Colebrook et al., 1936) in the treatment of puerperal fever.

The knowledge that women died of fevers consequent upon childbirth or miscarriage is of very great antiquity, and the course of childbed fever was accurately chronicled by Hippocrates (*Epidemics*), who described nine cases in the forty-two histories in Books I and III (Chadwick and Mann, 1950). Eight of these were fatal and one woman recovered after an eighty-day illness.

Also described are succinct histories of fatal infections following sore throat

(Case 7, Book III) and sore throat is mentioned as a symptom accompanying fever in the puerperium. Hippocrates noted much severe erysipelas early in the spring. Many cases were fatal and the patients often had a painful throat; some cases followed trivial wounds. There can be little doubt that streptococcal tonsillitis, other forms of streptococcal sepsis, and septicaemia are being described in these accounts, and that fatal infections clinically resembling those caused by streptococci were well known to the Hippocratic School.

Although puerperal fever loomed large in his practice, the cases described by Hippocrates occurred sporadically in the population, for there were as yet no lying-in hospitals. The evils these institutions aggravated showed in the appalling mortality recorded by Oliver Wendell Holmes (1843) and by Semmelweis (1861), both of whom wrote tracts on the contagiousness of childbed fever, its aetiology, concept, and prophylaxis. Their contribution to safe obstetrics was great, and their observations preceded the discovery of the causative agents by as much as fifty years. Wendell Holmes was to say, when a very old man, 'Others had cried out against the terrible evil before I did, but I think I shrieked my warning louder and longer than any of them . . . before the little army of microbes was marched up to support my position' (Morse, 1896). Both physicians recognised puerperal sepsis as a communicable disease, conveyed by the unclean hands of the examiner, or accoucheur; both recommended handwashing, and, variously, the donning of clean garments and the use of hand disinfectants when attending lying-in patients. In Semmelweis's case, the effect was remarkable, for the mortality which in May had been 12·24 per cent, fell in June to 2·38 per cent, and in July to 1·20 per cent, thus bringing it into line with the figures then current for British maternity units, whose practice was greatly envied on the continent of Europe. Semmelweis based part of his data on the clinical records of the British Lying-in Hospital in London, dating from 1749, the traditional date for the foundation of the hospital later to be known as Queen Charlotte's.

By 1900, figures for crude maternal mortality ran at 13·4 per 100,000 population, to 3·5 per 100,000 in 1947 (Major, 1954). Over the same period the death rates from scarlet fever were also declining.

Because it is easily recognised clinically, scarlet fever has long been used as the index disease for streptococcal sepsis of all types. Fluctuations in its incidence and severity are likely to indicate trends in the virulence of the infecting microbe, and, as the source of the infection in puerperal sepsis is ultimately a streptococcal sore throat, figures for scarlet fever are relevant to obstetric practice. They also reflect the likely reservoir of infection for streptococcal peritonitis.

In attempting to assess the value of any single therapeutic or preventive

measure in medicine, some consideration must be given to temporal fluctuations in the severity of the disease. In Sydenham's day (1624–1689) scarlatina was a mild disease associated with a rash but with no other signs. From the seventeenth century onwards its character changed: acute toxic pharyngeal symptoms became more important than the actual rash and at the end of the eighteenth century epidemics with high mortality rates occurred all over Europe. During the past eighty years its virulence has steadily declined, but in many countries scarlet fever is as common as ever it was; the alteration lies only in its fatality (Paul, 1964). The natural decline of streptococcal sepsis is usually illustrated by figures pertaining to deaths from scarlet fever. A WHO report (1954) suggests that the effects of prontosil and the sulphonamides, introduced in 1936, are discernible in the steady reduction in mortality from scarlet fever that occurred after this date in the USA. The effect of penicillin is probably discernible in the precipitous fall in the Registrar-General's figures for scarlet fever fatalities that occurred between 1940–1950.

TABLE 1. Deaths from scarlet fever, England and Wales, per million population, 1871–1950*

1871–1880	720
1881–1890	340
1891–1900	160
1901–1910	110
1911–1920	46
1921–1930	23
1931–1940	11
1950	0·7

* Data compiled by Paul, H. (1964)

The death rate, which had been declining almost in geometric regression over preceding decades, fell very steeply in this decade (Table 1). The virulence of the principal pathogen responsible for puerperal sepsis has declined since the beginning of the century; over the same period improvements in hygiene, and in social services and community care, have reduced the mortality from communicable disease.

The misery of the industrial poor of England was documented by Engels (1845) who referred to scarlet fever as a disease that brought most frightful devastation into the ranks of the working class. Reports of the Factories Inquiry Commission contemporaneous with Engels showed that in Manchester not quite 32 per cent of children of all classes died before the fifth year, while

in the labouring classes the figure reached 57 per cent. The urban death rate from scarlet fever was four times higher than that for rural districts. Although he did not write of childbed fever, Engels wrote that women not only worked 12 to 13 hours daily in a standing position up to the day of delivery, but were sometimes delivered on the factory floor, and returned to work within three days of confinement. Many a heroine of Victorian fiction died in childbirth, Oliver Twist's mother among them. Death in infancy and childbirth was commonplace in nineteenth century England.

It is against this multifactorial background that the effect of penicillin and related drugs on the practice of obstetrics and gynaecology must be considered.

From 1932 to 1939 Colebrook and his associates studied the aetiology of puerperal sepsis in the Isolation Block, built especially for this purpose and attached to Queen Charlotte's Maternity Hospital on the hospital's present site at Goldhawk Road, Hammersmith. In 1932, a third of all maternal deaths occurring in that hospital were ascribed to sepsis. Maternal sepsis was more common following operative delivery, and its rate was higher in patients admitted as emergencies. Some two per cent of all women suffered from serious postpartum morbidity, with pyrexia in excess of 101°F (Table 2); they were usually transferred to the Isolation Block, where they joined seriously ill

TABLE 2. Data from report of Queen Charlotte's Maternity Hospital (Marylebone Road, N.W.1) and Invermead Overflow Home, for 1932

Total maternal mortality	15	6·3/1000
Mortality from sepsis	5	2·1/1000
Mortality from sepsis excluding emergencies	2	0·9/1000
Maternal morbidity (serious)	59	2·1%

women admitted from other hospitals or from the care of private practitioners. Very careful records were maintained by Colebrook and his colleagues and were embodied in their annual reports. One of the more remarkable features of these reports is the consistent manner of recording data. For four years before the introduction of sulphonamides, the mortality rate from puerperal sepsis ran at a steady 11 to 12 per cent. The records were meticulously analysed and Table 3, based on Colebrook's data for 1932, shows the relationship of mortality to the presence of *Streptococcus pyogenes* as the aetiological agent, and to the morbid anatomical extent of the lesions. Provided the infection remained confined to the vagina, perineum or uterus, the women recovered. If general peritonitis or septicaemia supervened, the mortality rose to almost

TABLE 3. Relationship of mortality in puerperal fever to *Streptococcus pyogenes* and morbid anatomical extent of lesions (from Colebrook's data, 1932). Based on 251* cases of puerperal fever of whom 23* died (11·2%)

Infection limited to vagina, perineum or uterus	Nil
General peritonitis	68·2%
General peritonitis; *Str. pyogenes*	78%
Septicaemia	70%
Septicaemia; *Str. pyogenes*	98%
All infections with *Str. pyogenes* irrespective of extent of lesions	21·1%

* *Str. pyogenes* was isolated from 36% of all patients and from 68% of those who died.

70 per cent; and if the cause of peritonitis or septicaemia was *Str. pyogenes*, the mortality rose to 80–100 per cent. The overall mortality from streptococcal sepsis was of the order of 20 per cent. These figures, almost identical with those of succeeding years, illustrate the dangerous nature of streptococcal puerperal sepsis, and the hopelessness of palliative treatment in the pre-antibiotic era if the organism invaded the bloodstream or the tissues, as it was very likely to do. Table 4 shows the distribution of microbes in cases of septicaemia, and illustrates that streptococci were the organisms most frequently isolated from the bloodstream.

TABLE 4. Distribution of microbes in 27 cases of septicaemia occurring in 251 cases of puerperal fever (from Colebrook's data, 1932)

Streptococcus pyogenes	14
Anaerobic streptococci	9
Other streptococci	1
Bacillus coli	1
Salmonella paratyphi B	1
Unidentified bacillus	1
Total	27

TABLE 5. Queen Charlotte's Maternity Hospital reports 1932–1968: puerperal sepsis

Mortality rates expressed as percentages	
1932	11·2
1935*	11·1
1937	4·9
1938	3·9
1947	Nil
1968	0·8†

* Prontosil first used January, 1936
† One death, associated with *Cl. welchii*

In January 1936, Colebrook and Kenny began to use prontosil in the treatment of puerperal sepsis; later they used sulphonamides. Table 5 shows the tremendous reduction in mortality that occurred between 1935 and 1937 as a result of treatment with these chemotherapeutic agents. Although the mortality fell still further in 1938, and in the first three quarters of 1939, it

did not fall to nil until the bactericidal penicillin was used towards the end of the war. This is no more than would be expected, since the use of bacterio-static agents would be unlikely to prevent entirely the spread of bacteria beyond the genital tract proper. Effective as the sulphonamides were, they did not completely reduce the mortality in puerperal sepsis. However, widespread and prompt use of penicillin reduced the mortality rate in streptococcal puerperal sepsis to nil. Fatalities now occurring in obstetric practice are usually associated with clostridial sepsis, or with failure to institute antibacterial therapy sufficiently promptly. About ten deaths a year attributable to puerperal and post-abortal sepsis occur in England and Wales.

A further effect of penicillin, and one that was not achieved through use of the chemotherapeutic agents, was the virtual elimination of *Str. pyogenes* as a cause of puerperal sepsis (Table 6). Again, this can be attributed to the bactericidal effect of penicillin.

TABLE 6. Queen Charlotte's Maternity Hospital Reports 1932–1968: puerperal sepsis

Percentage incidence of *Str. Pyogenes*	
1932	34·6
1935	34·0
1937	35·7
1938	36·9
1947	0·013
1968	Nil
Prontosil first used January, 1936	

During the sulphonamide era, the incidence of *Str. pyogenes* as a cause of puerperal sepsis remained of the same order as in the years preceding intro-duction of the chemotherapeutic agents. After the war, *Str. pyogenes* became an unusual cause of puerperal sepsis, and the organism is now rarely encountered in obstetric practice. The last outbreak of streptococcal sepsis occurred at Queen Charlotte's Hospital in 1952 (Gibson and Calman, 1953). On a national scale, this effect can be seen in the decline in the notifications of puerperal fever and pyrexia that occurred after the introduction of penicillin (Fig. 1). This graph (Barber, 1960) was compiled from the Registrar-General's figures. After 1950, the criteria for notification of puerperal pyrexia changed; and notification has now been abandoned. Nothing could testify more elo-quently to the conquest of puerperal sepsis.

Valvular disease of the heart is one of the sequelae of infection with *Str.*
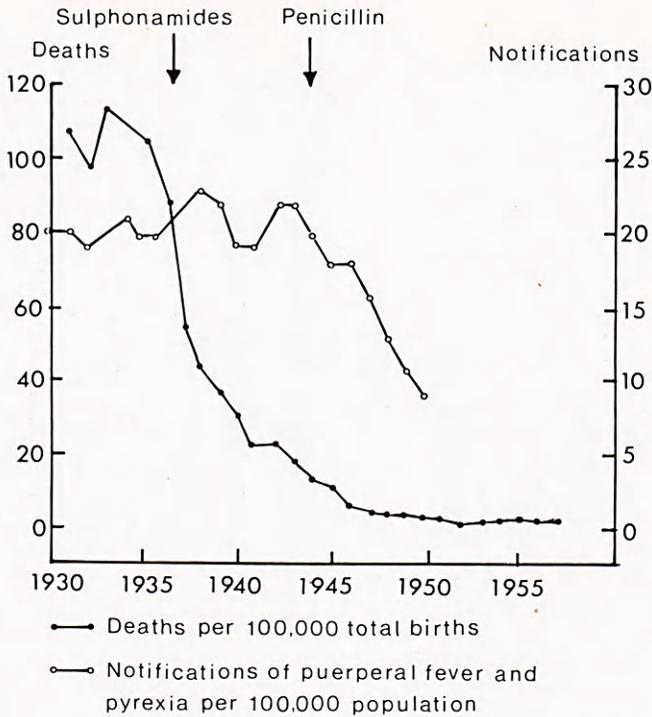
Fig. 1. Infection during childbirth and the puerperium (*after* Barber, 1960).

pyogenes, and is itself a primary cause of maternal mortality. Figure 2 shows the incidence of cardiac disease of all types over the thirty-six year period spanning the introduction of the sulphonamides and of the antibacterial antibiotics. Mitral stenosis is taken as the index disease of rheumatic carditis. In 1933, the maternal mortality in cardiac disease was higher than that obtaining in puerperal sepsis; in 1946, half the maternal deaths in the hospital were associated with rheumatic carditis. Cardiac disease was accompanied by a high foetal and perinatal mortality. The proportion of cases of mitral stenosis seen in the hospital has steadily declined, and now it is a rarity in obstetric practice. Figure 3 shows that over the years the percentage of women with mitral stenosis presenting as primipara has declined; none are now seen.

The mean age of the multigravida rose, but is falling now, as those affected leave the childbearing years. These figures indicate that there are fewer new cases of rheumatic carditis, and that such patients as are seen in our clinics have had the disease for many years. There is, as yet, no reduction in the Registrar-General's figures for mortality from rheumatic heart disease,
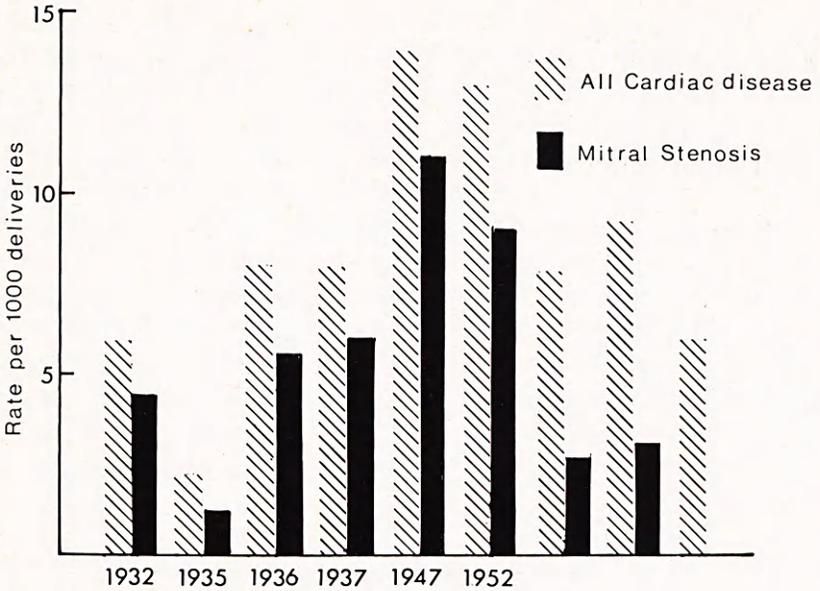
Fig. 2. Data on cardiac disease from reports on Queen Charlotte's Maternity Hospital 1932–1968.

but the affected live longer, because of advances in both medicine and surgery. Rheumatic carditis is a declining disease in obstetric practice, and this is probably attributable to the use of bactericidal agents in the treatment of streptococcal disease, as well as to the reduction of the reservoir of infection in the community consequent on antibiotic therapy.

There has been a parallel reduction in deaths attributable to sepsis in the gynaecological practice of the Chelsea Hospital for Women (Table 7). While many of the patients who died formerly had advanced malignant disease complicated by peritonitis or pneumonia, deaths associated with sepsis are now uncommon.

There can be scant doubt that the effect of the penicillins in reducing maternal and gynaecological morbidity and mortality has been great. Thirty years ago, streptococcal sepsis leading to peritonitis or septicaemia with an almost uniformly fatal consequence was common. It is seldom encountered today. Not only has the mortality of streptococcal disease declined as a result of penicillin treatment; the incidence of serious disease has also
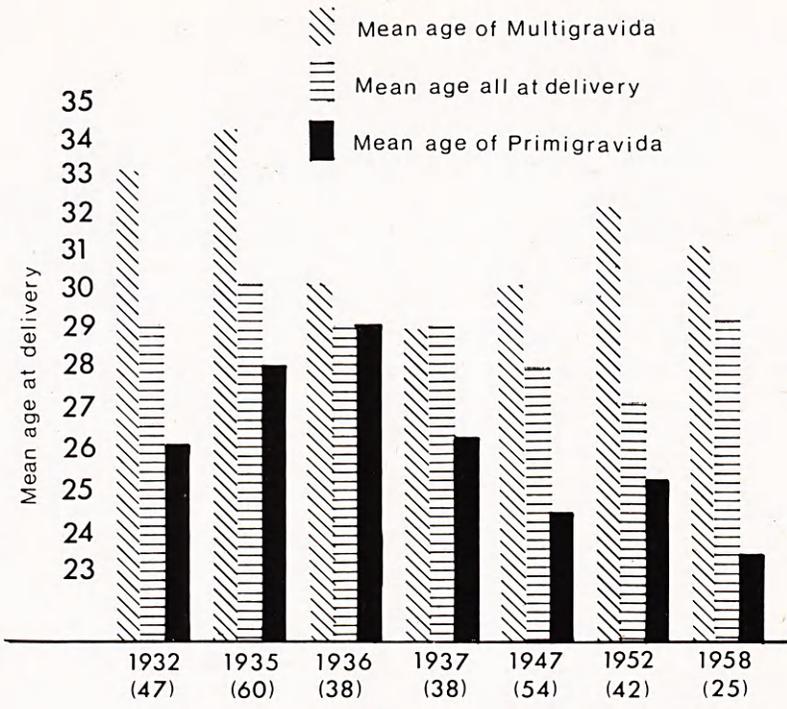
Fig. 3. Data on mitral stenosis from reports on Queen Charlotte's Maternity Hospital 1932–1958.

TABLE 7. Chelsea Hospital for Women Reports 1930–1956

Deaths associated with sepsis*		
1930	4	20% all deaths
1941	12	42% all deaths
1945†	12	33% all deaths
1951	5	35% all deaths
1956	Nil	Nil
*Principally pneumonia or peritonitis † Penicillin stated to be used		

fallen. Penicillin and allied drugs have reduced the incidence of dangerous streptococci in the population, and thus the reservoir of infection, to an extremely low figure. *Str. pyogenes* (Lancefield Group A), which formerly accounted for some 35 per cent of all cases of puerperal sepsis, is seldom isolated from women with elevation of the temperature in the puerperium

(Hurley, 1969). Even when it is, it causes the obstetrician no more than a passing concern, for with modern therapy the prognosis is excellent.

The effect of penicillin on the reduction of incidence of rheumatic carditis is less easy to establish, but its incidence in maternity units is in marked decline, and this has been accompanied by a substantial reduction in maternal and perinatal mortality. The reduced number of cases of rheumatic carditis is probably attributable to a true decline in the incidence of streptococcal tonsillitis and scarlet fever in the population as a whole, as a result of widespread use of bactericidal antibiotics. It is probably independent of the natural decline in the virulence of the haemolytic streptococcus, for in countries where bactericidal agents are not used extensively, it is only the mortality from streptococcal disease that is declining, and not its incidence (Paul, 1964).

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