Medical History

Puerperal fever, the streptococcus, and the sulphonamides, 1911-1945

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The downward trend in death rates in Britain between the second half of the nineteenth century and the mid-1930s, especially for deaths from infective disorders, is well known. It is now generally agreed that the decline was largely due to improvements in social and economic conditions, primarily in hygiene and nutrition, rather than medical care. Increased immunity or decreases in the virulence of micro-organisms may have played a part in a few infectious diseases, but it is considered unlikely that they were important factors in the general reduction in the death rate.¹

If social and economic improvements were responsible for the fall in the general death rate the same factors should have produced a fall in maternal mortality. In fact the fall in maternal deaths should have been even steeper because of the additional factor of advances in obstetric care. Obstetrics differed from general medicine in this respect: measures were introduced between the late nineteenth century and the 1930s that were capable of reducing mortality. These included the techniques of antisepsis and asepsis, introduced in the 1870s and 1880s; caesarean section as a safe technique for certain obstetric emergencies after 1900; the Midwives Act of 1902; and improvements in the teaching of obstetrics and the growing recognition of the importance of antenatal care in the 1920s and 1930s.

Paradoxically, maternal mortality refused to fall. Instead, it remained on a plateau from the 1850s to the mid-1930s. Arnold Lea of Manchester remarked in 1910: "In the five years 1851-5 the puerperal death rate from all causes [in England and Wales] was 4.9 per 1000 [births], and in the five years ending 1906 it still amounted to 4.2 per thousand" and "we do no violence to the statistics if we put down the septic [puerperal fever] mortality in England and Wales at between 3000 and 5000 per annum." He believed that most septic deaths were preventable and would soon be prevented.² But a quarter of a century later, in the five years ending in 1934, the maternal mortality was exactly the same, 4.2 per 1000 births.

The undiminished maternal mortality, which became a public and political scandal by the 1920s, was not confined to England and Wales. In Scotland maternal mortality actually increased between 1900 and 1930.³ In the United States, too, maternal mortality remained more or less constant at one of the highest recorded levels in the world, although a large and rapidly growing proportion of deliveries after 1920 took place in hospital under the care of specialist obstetricians (table I).^{4,7} Even in Denmark, Holland, and Scandinavia, where low maternal mortality was a constant reproach to the British and Americans, rates tended to stay level rather than to fall.^{5,8}

Some of these aspects of the history of maternal mortality were

discussed in two previous papers.^{9,10} This paper is concerned specifically with puerperal fever: why the death rate from puerperal fever remained so high until the mid-1930s and what led to the subsequent steep and sustained fall. The chronological boundaries are 1911, when the International List of Causes of Death (the ICD classification) was adopted by Britain, and 1945, when the profound fall in maternal mortality was firmly established and the mortality had fallen to only one third of the rate in 1934.

TABLE I—Maternal mortality in certain countries, 1920⁵

Country	Maternal mortality from all causes (per 1000 live births)
Denmark	2.35
The Netherlands	2.42
Sweden (1918)	2.58
Norway (1919)	2.97
Uruguay	3.38
Japan	3.53
Finland	3.60
Italy	3.67
Union of South Africa	4.10
England and Wales	4.33
Spain	5.01
Germany (1919)	5.15
Ireland	5.53
Belgium	6.09
Scotland	6.15
New Zealand	6.48
France	6.64
Chile	7.48
United States	7.99

Puerperal fever, erysipelas, and scarlet fever

If maternal mortality is separated into its two main divisions—deaths from puerperal fever and other maternal deaths grouped together as "accidents of childbirth"—little variation is seen in deaths from accidents from 1911 to 1934 and then the rate began to fall gradually (fig 1). Deaths from puerperal fever, on the other hand, showed more variation, with peaks of high mortality in 1920, 1930, and 1934 and low mortality in 1913 and 1918. After 1934 deaths from puerperal fever fell so steeply that 78% of the total reduction in maternal mortality in England and Wales between 1934 and 1940 was due to the reduction in deaths from puerperal fever. Similar trends occurred in Scotland.³

This sudden, steep, and sustained fall in deaths from puerperal fever after the long period of high mortality is one of the most remarkable events in the history of obstetric care. Puerperal fever was not only the cause of the appallingly high death rates in nineteenth century lying in hospitals, it was until recently the single most common cause of maternal deaths, accounting on average for about 40% of total maternal mortality. Most deaths were due to

infection with the β haemolytic streptococcus Lancefield group A, also known as *Streptococcus pyogenes*.¹¹⁻¹³ An investigation of 196 severe cases of puerperal fever in 1931 showed that 76% of high vaginal swabs, 87% of positive blood cultures, and 84% of cultures of pus grew *S. pyogenes*. The domination of puerperal fever by this organism suggested that a comparison of secular changes in the death and notification rates of puerperal fever, erysipelas, and scarlet fever might be valuable.

Table II and figure 2 show the remarkably close relation between mortality from erysipelas and puerperal fever and figure 3 the similar but less striking link between scarlet fever and puerperal fever. A similar association between the three diseases occurred in Scotland between 1911 and 1945, and also in England in the 20 year period 1860-79 (table III and figure 4) when the death rate from scarlet fever was very high, reaching 145.7 per 100 000 persons under the age of 15 in 1889 and falling to 15.9 in 1911.¹⁴

What this seems to demonstrate is the prime importance of variations in the prevalence of the streptococcus in the population.

FIG 1—Total maternal mortality and mortality from puerperal fever and accidents of childbirth in England and Wales, 1911-45.

TABLE II—Death rates per 100 000 people: scarlet fever, erysipelas, and puerperal fever, and deaths from puerperal fever per 1000 births. England and Wales, 1911-45

Year	Scarlet fever (per 100 000)	Erysipelas (per 100 000)	Puerperal fever (per 100 000)	Puerperal fever (per 1000 births)
1911	5.2	2.7	3.7	1.43
1912	5.4	2.5	3.5	1.39
1913	5.7	2.2	3.2	1.26
1914	7.7	3.1	3.9	1.55
1915	6.6	3.0	3.5	1.47
1916	3.9	2.1	3.3	1.38
1917	2.2	1.7	2.7	1.31
1918	2.9	1.7	2.5	1.28
1919	3.4	1.8	3.2	1.67
1920	3.8	2.2	4.6	1.81
1921	3.4	1.9	3.9	1.38
1922	3.6	1.8	2.8	1.38
1923	2.6	1.6	2.6	1.30
1924	2.3	1.7	2.6	1.39
1925	2.5	2.1	2.9	1.56
1926	1.7	2.2	2.8	1.60
1927	1.5	2.0	2.6	1.57
1928	1.5	2.3	3.0	1.79
1929	1.8	2.6	2.9	1.80
1930	1.9	2.6	3.1	1.92
1931	1.4	2.5	2.6	1.59
1932	1.3	2.5	2.5	1.55
1933	1.8	2.9	2.6	1.75
1934	2.4	3.0	3.0	1.95
1935	1.4	2.6	2.5	1.61
1936	1.2	2.4	2.1	1.34
1937	0.85	1.4	1.5	0.94
1938	0.86	1.0	1.3	0.86
1939	0.52	0.59	0.96	0.74
1940	0.37	0.51	0.81	0.54
1941	0.32	0.45	0.69	0.47
1942	0.32	0.34	0.68	0.42
1943	0.32	0.29	0.66	0.39
1944	0.25	0.28	0.52	0.28
1945	0.2	0.3	0.24	0.24

Source: Annual reports of the Registrar General, Registrar General's Statistical Review, and annual reports of the Chief Medical Officer of the Ministry of Health.

FIG 2—Death rates from erysipelas per 100 000 people of all ages and deaths from puerperal fever per 1000 births, England and Wales, 1911-45. Source as in table II.

FIG 3—Death rates from scarlet fever per 100 000 people of all ages and deaths from puerperal fever per 1000 births, England and Wales, 1911-45. Source as in table II.

This, rather than changes in standards of obstetric care or in the economic circumstances of the population, seems to have determined the mortality from puerperal fever. But why was there a closer association between death rates for erysipelas and puerperal fever than between rates for puerperal fever and scarlet fever? The probable explanation is that erysipelas and puerperal fever are essentially wound infections, while scarlet fever—a respiratory tract infection of children—has a different natural history. The simultaneous decline in deaths after 1934 from all three diseases is, as will be shown, particularly important.

The existence of a close relation between puerperal fever and erysipelas had been recognised for a long time. It was important in the fierce debate from the 1780s to the 1880s concerning the contagiousness of puerperal fever. The central feature of the debate was the risk of a midwife or doctor carrying puerperal fever from one obstetric case to another. A second component, often overlooked by historians, was the possible connection between puerperal fever and other diseases. Erysipelas, typhus, and diphtheria (which was confused with scarlet fever until the mid-nineteenth century) were all candidates, but erysipelas held pride of place from the late eighteenth century.¹⁵ Alexander Gordon of Aberdeen in 1795 was the first to provide convincing evidence both of the contagiousness of puerperal fever and of its close relation to erysipelas.¹⁶

In the prebacteriology period there was no more important debate in the practice of obstetrics. Few deaths were as poignant as those from puerperal fever. Women dreaded the pain and danger of labour itself. Having survived the ordeal of labour, it was the cruellest of tragedies to die only a few days later from puerperal fever. It was a family disaster for which the doctor or midwife was

often blamed. Indeed, a series of such deaths could ruin the reputation of a practitioner. Most, whatever their private opinions about contagion, knew it was wise after attending a case of puerperal fever or erysipelas to change their clothes and wash thoroughly before attending the next patient in labour.¹⁷ For instance, Dr Elkington of Birmingham invariably followed this rule, except for the one occasion when, just after attending a case of erysipelas, he was called urgently to a case of placenta praevia. He had no choice, he wrote, but to: "turn and deliver" without loss of time." (Internal version and pulling down a leg to plug the placenta with the "half breech" was the standard and often successful treatment for placenta praevia.) "She was confined June 15th," he continued,

TABLE III—Deaths per million people living: scarlet fever, erysipelas, and puerperal fever, and mortality from puerperal fever per 1000 live births 1860-79 expressed as the annual death rates and as the percentage variation for each year above or below the mean value for the whole 20 year period, England and Wales

Year	Scarlet fever		Erysipelas		Puerperal fever		Puerperal fever	
	Deaths	%	Deaths	%	Deaths	%	Mortality per 1000 births	%
1860-79*	843		91		65		1.81	
1860	493	-41	85	-7	50	-23	1.44	-20
1861	456	-46	78	-14	45	-30	1.27	-30
1862	738	-12	76	-16	47	-28	1.32	-27
1863	1498	+78	94	+3	57	-12	1.56	-14
1864	1443	+71	102	+12	72	+11	2.00	+10
1865	852	-1	95	+5	64	-1	1.78	-2
1866	556	-34	80	-12	57	-12	1.59	-12
1867	580	-31	68	-25	50	-23	1.39	-23
1868	1020	+21	91	0	56	-14	1.52	-16
1869	1275	+51	87	-5	54	-17	1.53	-15
1870	1461	+73	96	+6	67	+3	1.88	+4
1871	822	-3	99	+9	65	0	1.81	0
1872	521	-38	78	-14	61	-5	1.70	-6
1873	567	-32	88	-3	75	+15	2.10	+12
1874	1062	+26	144	+58	132	+103	3.63	+100
1875	857	+2	127	+39	105	+61	2.94	+62
1876	696	-17	97	+7	72	+11	1.97	+9
1877	587	-30	85	-7	59	-9	1.63	-10
1878	694	-18	76	-16	57	-12	1.59	-12
1879	677	-20	77	-15	58	-11	1.66	-8

*Mean annual number of deaths for the period 1860-79.

Source: Annual reports of the Registrar General for England and Wales.

FIG 4—Deaths per million people living: scarlet fever, erysipelas, and puerperal fever; and mortality from puerperal fever per 1000 live births, 1860-79; shown as the mean value and as the percentage variation for each year above or below the mean for the period of 20 years, England and Wales. Source: reports of the Registrar General for England and Wales.

"and the next day was very comfortable, was attacked with fever on the 17th and died on the 20th."¹⁸ Such anecdotes were common and can be found in the many publications which emphasised both the contagiousness of puerperal fever and the link with erysipelas.¹⁹⁻²⁹

In 1875 Longstaff, using an epidemiological approach, provided the most convincing evidence "that the curves of [the mortality from] erysipelas and puerperal fever are practically identical . . . I confess that I find it difficult to avoid the conclusion that they are both due to one poison."³⁰ It was a perceptive conclusion, foreshadowing the discoveries of the 1880s which provided evidence of the specific pathogenicity of the streptococcus³¹ and final proof of the contagiousness of puerperal fever and the link with erysipelas. But the triumphs of bacteriology and laboratory medicine tended to eclipse the importance of epidemiological evidence. Puerperal fever was studied in intense detail as a problem in bacteriology and antisepsis; hardly ever was it studied in the context either of the past or of streptococcal infections in general.

A lack of historical depth and relative neglect of epidemiology are notable features of most of the large volume of work on maternal mortality published in the first half of this century. When maternal mortality fell for two or three consecutive years there was rejoicing; maternal mortality was being conquered and doctors took the credit. When it was followed by a rise in mortality there was gloom, and doctors argued who was to blame. Rarely did they look back at the graphs of previous decades or identify the vagaries of the levels of streptococcal infection. Geddes in 1912 was almost alone in showing the importance of a broad approach to the problem of puerperal fever by showing the link between a high rate of industrial accidents (and thus of infected wounds) and a high rate of puerperal fever and erysipelas in mining and industrial areas compared with rural ones.³² By doing so he provided an explanation for two puzzling features of puerperal fever: the high rate in industrial areas compared with rural and residential areas and the higher rate in cases attended by general practitioners (who were constantly in contact with erysipelas and scarlet fever) than in cases attended by midwives. Geddes's work won a prize but never received the attention it deserved.³³

Continuing high death rate from puerperal fever

Why, then, despite asepsis and antisepsis, was there no appreciable fall in deaths from puerperal fever until the mid-1930s, and then such a profound and sustained decline in the death rate? The standard answer to the first part of the question—and there is no reason to dismiss it—was poor standards of practice.⁹ Unnecessary intervention in normal labours on a huge scale was accompanied by inadequate antisepsis and the neglect of the more difficult techniques of asepsis. "Practitioners of midwifery who use antiseptics perfunctorily, and even omit to roll up coat-sleeves when making a vaginal examination" was a common accusation.³⁴ Accounts of "failed forceps" and major injuries to the vagina and cervix were disturbingly frequent.³⁵⁻³⁶ Only a few practitioners may have been so negligent, but even the scrupulous practitioner was, through no fault of his own, unaware of the true sources of most cases of puerperal infection. Many believed infection was "endogenous" (originating from an infected cervix) and therefore unavoidable. Exogenous infection, it was thought, could easily be avoided by ordinary washing and the use of antiseptics. It was a common belief, fortified by observing the techniques of the teaching hospitals in the 1920s and 1930s, that the standard of asepsis and antisepsis required in obstetrics was much lower than in general surgery.³⁷

Against that background the importance of the work of Lancefield, Smith, Griffiths, and Leonard and Dora Colebrook, which led to new methods of identifying and typing strains of streptococci, making it possible to trace the exact source of infection, can be appreciated.³⁸⁻⁴¹ This research led to three important findings: that endogenous infection was rare; that the most common source of infection in puerperal fever was droplet infection from a doctor, midwife, or nurse who was either asymptomatic or suffering from a trivial complaint such as a sore throat; and that at

least 7% of the apparently healthy population (and sometimes as many as 40%) were asymptomatic carriers of *S pyogenes*. It was also shown that minor disorders such as "sore throats, sinus infections, so called colds, and influenza, impetigo, and small septic sores or burns" were a potent source of streptococcal infection.³⁹

In one investigation the Colebrooks found that in 48 cases of puerperal fever the source of infection was an attendant at the birth in 24 cases, a member of the patient's household in nine cases, the patient herself in six cases, and uncertain in nine.³⁹ The honest, if not reassuring, answer to the patient who asked: What is the cause of puerperal fever? was "Usually your doctor or midwife; sometimes yourself, your family, or friends." The likelihood that an exceptionally high carrier rate may have been an occupational hazard of general practice was never, as far as I can discover, put to the test.⁴²

TABLE IV—Deaths as a percentage of notifications: scarlet fever, erysipelas, and puerperal pyrexia. England and Wales, 1918-45

Year	Scarlet fever	Erysipelas	Puerperal pyrexia
1918	2.1	4.8	70.0
1919	1.5	4.2	57.3
1920	1.1	5.2	59.7
1921	0.9	5.5	52.9
1922	1.3	5.3	50.5
1923	1.2	5.0	50.5
1924	1.0	5.2	46.6
1925	1.1	5.7	46.3
1926	0.8	5.8	25.0*
1927	0.7	5.5	13.6
1928	0.5	5.4	15.0
1929	0.6	5.8	14.5
1930	0.6	5.6	15.1
1931	0.6	6.6	13.0
1932	0.6	6.8	13.0
1933	0.5	6.6	13.4
1934	0.6	7.1	14.3
1935	0.5	6.2	12.3
1936	0.5	6.0	10.2
1937	0.4	3.8	6.7
1938	0.4	2.5	6.0
1939	0.3	1.7	6.0
1940	0.2	1.6	4.4
1941	0.2	1.5	3.9
1942	0.1	1.2	3.3
1943	0.1	1.0	3.3
1944	0.1	1.1	2.7
1945	0.1	1.2	

*The apparent abrupt fall in fatality rates for puerperal fever in 1926-7 is an artefact due to the introduction of a new definition of puerperal fever.⁴⁷
Sources: Annual reports of the Registrar General and Registrar General's Statistical Reviews.

It follows that even if all practitioners were conscientious the strategies for preventing puerperal fever in the period between the two world wars were inadequate. Lack of knowledge combined with the prevalence of the highly dangerous haemolytic streptococcus made the prevention of puerperal infection much more difficult than it is today. Nothing short of scrupulous asepsis at every labour (which was practised with conspicuous success in a few hospitals⁴³) would have had a major impact on the death rate. This was recognised by the newly founded College of Obstetricians when in 1929 its maternal mortality subcommittee recommended masks and sterilised gowns and rubber gloves ("preferably reaching to the elbows") at every delivery.⁴⁴ Such extreme measures were seldom practised even in well known hospitals and considered quite impractical for domiciliary midwifery.

Before we are too quick to condemn our predecessors for negligent practice we must remember the ubiquity of *S pyogenes* and consider the possibility that the undiminished mortality from puerperal fever was due to an increase in streptococcal virulence which overcame all attempts at better aseptic techniques. There is, after all, compelling historical evidence that the virulence, as opposed to the prevalence, of the haemolytic streptococcus varied widely in the past.⁴⁵⁻⁴⁶ There are well documented periods when scarlet fever was common but very mild, and others—1860-90, for example—when it was common but deadly. Erysipelas in the eighteenth and nineteenth centuries often appeared together

with puerperal fever in epidemics that would sweep through a community like a minor plague and then subside.^{16 17 19} By the beginning of this century compulsory notification of some infectious diseases (introduced in 1899) makes it possible, at least in theory, to identify changes in virulence by means of the case fatality rate (deaths as a percentage of notifications) when there was no treatment that affected the fatality rate (see table IV).

Unfortunately, puerperal fever was defined for notification purposes by the imprecise term "puerperal sepsis" and under-notified on a large scale.³² It was not until 1926 that it was redefined as puerperal pyrexia—and fever occurring within 21 days of childbirth in which a temperature of 100.4°F (38°C) or more was sustained or recurred during a period of 24 hours.⁴⁷ There was a delay in adopting the new definition so that the notification statistics of puerperal fever before 1930 are virtually useless. Data on erysipelas and scarlet fever provide an apparent contradiction. The fatality rate of erysipelas rose slightly from 1918 to 1935, suggesting an increase in virulence; but the rate for scarlet fever continued to decline as it had done since the late nineteenth century. Introducing active and passive immunisation against scarlet fever in the 1920s may conceivably have played some part in reducing mortality.⁴⁸ But, in general, the evidence suggests that variations in the prevalence rather than the virulence of streptococcal infections account for the peaks in mortality from puerperal fever in 1920, 1930, and 1934. An abrupt and major decline in streptococcal virulence after 1934 has been suggested as one of the explanations for the fall in maternal mortality. Was it this, or the sulphonamides, or a combination of factors?

Sulphonamides and the fall in maternal mortality

Although the obvious explanation for the sudden fall in deaths from puerperal fever is the introduction of the sulphonamides, it has been disputed by several authors,⁴⁹⁻⁵³ who have argued convincingly that the chronology is wrong because the fall in mortality began too soon. Domagk's work in Germany on Prontosil did not take place until 1935. By the time sulphonamides were generally available in Britain the decline in mortality was firmly established. The Medical Research Council trial of sulphonamides in puerperal fever, which took place at Queen Charlotte's Hospital in the first half of 1936, is believed to be the first time sulphonamides were used in Britain. The results of this trial were not published until December 1936, and the number of patients treated was, of course, too small to affect the national statistics.⁵⁴

Other explanations for the fall in maternal mortality have included blood transfusion, the introduction of flying squads, improved socioeconomic conditions after the depression, better obstetric care in light of new knowledge, and an improved maternity service as a result of wartime measures. Undoubtedly all of these played a part, but they did so gradually and for the most part after 1940. There may have been a decline in streptococcal virulence, but none of the other factors can explain the early phase of the sudden and profound fall in deaths from puerperal fever. Neither can the introduction of the sulphonamides if 1935 is accepted as the year in which the tide was finally turned and a new and appreciable fall in maternal mortality began.

It can be shown, however, that the first notable year in the fall in mortality was 1937, not 1935. The death rates from puerperal fever were lower in 1913 and 1918 than in 1935 and 1936. Only for 1937, when deaths from puerperal fever reached a new low level, can it be said with confidence that a new factor or factors came into operation; and the same argument applies to deaths from erysipelas and scarlet fever, which also fell lower than ever before in 1937. In short "1937 [was] the first year of sustained decline" in deaths from puerperal fever.^{55 56}

The importance of examining the death rate from puerperal fever in the context of streptococcal infections as a whole now becomes obvious. The pinpointing of 1937 as the start of the decline, and the concurrent fall not only in the total number of deaths but also in the fatality rate from puerperal fever, erysipelas, and scarlet fever, seem to narrow the choice of factors either to treatment

with sulphonamides or to a sudden and unprecedented fall in streptococcal virulence. If the sulphonamides were responsible it is necessary to show that they were generally available and widely used in 1937. At first sight this seems unlikely. Today it would be uncommon for a drug with potentially serious side effects to be released within a few months of the first clinical trial, but not in the 1930s.

Sulphonamides were used to prevent or treat puerperal fever in at least five hospitals in late 1936 and 1937, such as the Simpson Memorial Hospital in Edinburgh (where every patient delivered in 1937 was given a prophylactic course of either Prontosil or Proseptazine),⁵⁷ hospitals in London,^{51 58} Glasgow,⁵⁹ Belfast,⁴⁹ and Liverpool,⁶⁰ and almost certainly hospitals elsewhere. The sulphonamides were easy to manufacture, drug firms recognised their potential importance, and at least five proprietary brands were available for general use by the spring of 1937.

Prontosil rubrum, patented in 1932, was used extensively on the continent from 1935 onwards.⁶¹ Rubiazol (chlorhydrate de sulfamido-chrysoidine) was produced and marketed by Roussel in France and other European countries from May 1935 and used for the treatment of erysipelas, septicaemia, pleurisy and pneumonia, and puerperal fever (L A Tillman, Roussel Laboratories, personal communication). Supplies of this drug were restricted during the second world war, and it is notable that whereas maternal mortality declined steadily in Britain and the USA from 1939 to 1945, it remained level in France, Belgium, and Holland until 1946. In Britain May and Baker marketed Proseptazine (an oral sulphonamide) and Soluseptazine (for injection) in 1936.⁶² Sulphapyridine, which became a household name as M & B 693, was not produced until 1938⁶³; but in 1937 the available brands of sulphonamides included Rubiazol (Roussel), *p*-aminobenzene sulphonamide (sulphanilamide) marketed as Streptoside (Evans, Lescher and Webb), Sulphonamide P (British Drug Houses), Sulphonamide A&H (Allen and Hanburys), and Sulphonamide (Burroughs Wellcome).⁶⁴ Papers published in 1937 and 1938 advised the use of sulphonamides for the treatment of puerperal fever in general practice,⁶⁵⁻⁶⁸ and replies to a questionnaire on the use of sulphonamides in December 1937 showed that they were being used extensively in the treatment of puerperal fever in general practice as well as hospital practice.⁶⁹ Sulphonamides, which were used from the start in a wide range of infections (David E Smith, personal communication), were shown to be effective in the treatment of erysipelas in a well controlled trial of 312 cases carried out for the Medical Research Council in 1936-7.⁷⁰

Sulphonamides were therefore generally available, widely used, and known to be effective in the year in which deaths from puerperal fever, erysipelas, and scarlet fever reached the lowest level ever recorded. Hawkins and Lawrence in 1950 came to the cautious conclusion, endorsed by Taylor and Dauncey in 1954, that the introduction of the sulphonamides was "one of the rare situations which endorse the identification of an agency of major importance as contributory to a statistical trend."^{75 56} But the possibility of a simultaneous decline in streptococcal virulence should not be dismissed too readily. Although the evidence is largely anecdotal, experienced observers, including Colebrook, believed that the streptococcus became less dangerous after 1934 than formerly.^{50 51 54}

Nevertheless, the most likely hypothesis is, in this instance, the traditional explanation. The main factor responsible for the sustained fall in maternal mortality from 1937 to the early 1940s was the introduction of the sulphonamides. When, later on, penicillin, blood transfusion, better obstetric care, and so on played increasingly important parts in lowering maternal mortality they tended to eclipse the early but vital contribution of the sulphonamides. Whether the postwar decline in puerperal fever, scarlet fever, and erysipelas—and also in rheumatic fever and acute nephritis—was due to antibiotics or a decline in the prevalence and virulence of the streptococcus, and whether the use of antibiotics was responsible for changes in streptococcal prevalence and virulence, are questions of great interest which lie outside the scope of this paper.

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Lesson of the Week

Refeeding hypophosphataemia in anorexia nervosa and alcoholism

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Phosphate is important for cellular metabolism.¹ Body phosphate stores may become depleted during inadequate nutrition, and severe hypophosphataemia may ensue when metabolic demand for phosphate is subsequently increased acutely; this condition is termed the nutritional recovery syndrome.² We describe two such cases associated with anorexia nervosa and with severe alcoholism. Marrow suppression, anaemia, thrombocytopenia, neuroencephalopathy, convulsions, and cardiac effects occurred associated with acute hypophosphataemia.

Case 1

An 18 year old man with anorexia nervosa was admitted, having collapsed after alcohol ingestion. He weighed 29 kg. Pulse rate was 40/min, and blood pressure 100/70 mm Hg. Plasma glucose concentration was <1 mmol/l (normal 3.6-5.8), plasma phosphate concentration 1.34 mmol/l (normal 0.8-1.4), haemoglobin concentration 124 g/l, white cell count $15.4 \times 10^9/l$, and platelet count $316 \times 10^9/l$. He responded to intravenous dextrose, and a ward diet was instituted. After two days the plasma phosphate concentration fell to 0.45 mmol/l and after four days to 0.20 mmol/l. Haemoglobin concentration fell to 98 g/l, white cell count to $2.8 \times 10^9/l$, and platelet count to $41 \times 10^9/l$. Bone marrow was severely hypoplastic. No cause for the marrow suppression was found other than hypophosphataemia. Over two weeks of normal diet the plasma phosphate value rose to 0.64 mmol/l and full blood count returned to normal with a 5-7% reticulocytosis.

Three months later the patient relapsed and was readmitted weighing 27 kg. He was given a normal diet and gained 4 kg. After 10 days grand mal convulsions began, recurring over three days despite anticonvulsants. There were no focal neurological signs; conscious level remained depressed

The plasma phosphate concentration should be monitored for several days in any patient being refed after a prolonged period of inadequate nutrition

between convulsions. Plasma phosphate concentration was 0.07 mmol/l. Plasma glucose, calcium, and potassium concentrations and arterial oxygen tension were normal; plasma magnesium was 0.6 mmol/l (normal 0.7-1.3). Computed tomography showed some brain shrinkage only. Results of lumbar puncture were normal. An electroencephalogram was diffusely abnormal without epileptiform activity. Bone marrow was hypoplastic, haemoglobin concentration 84 g/l, white cell count $2.3 \times 10^9/l$, and platelet count $139 \times 10^9/l$ with no identifiable cause other than hypophosphataemia. After treatment with phenytoin and a ward diet the plasma phosphate concentration rose to 1.25 mmol/l and he recovered over 10 days. At follow up all haematological and biochemical analytes were normal.

Case 2

A 60 year old woman with longstanding alcohol dependency was admitted having collapsed. She lived alone and derived virtually all of her intake of energy from gin and wine. She was emaciated and jaundiced; pulse was 110/min and blood pressure 140/70 mm Hg and the liver was palpable four fingerbreadths below the costal margin. She was rational, oriented, and had no neurological abnormalities. Bilirubin concentration was 86 $\mu\text{mol/l}$, alkaline phosphatase activity 255 IU/l, and γ -glutamyltransferase activity 1504 IU/l. Sodium, potassium, and total carbon dioxide values were reduced at 131, 3.2, and 14.0 mmol/l respectively; glucose concentration was 6.1 mmol/l, and calcium 2.3 mmol/l. Plasma phosphate concentration was 0.30 mmol/l and magnesium 0.36 mmol/l. Liver biopsy showed cirrhosis, fatty change, and alcoholic hepatitis. She began a normal diet. Twenty four hours later the plasma phosphate concentration fell to 0.1 mmol/l, remaining so for 48 hours. She became progressively less well, with confusion, tachycardia, and widespread T wave inversion. She could not tolerate treatment by mouth and was given 100 mmol mixed phosphate solution (Polyfusor) intravenously over 48 hours by infusion pump, which raised the plasma phosphate concentration to normal (1.2 mmol/l). Plasma calcium and magnesium concentrations fell, necessitating separate infusions of calcium,

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