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What is This?

The use of historical controls and concurrent controls to assess the effects of sulphonamides, 1936–1945

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The introduction of the sulphonamides in the 1930s was seen as an immensely important advance in the treatment of a wide range of bacterial diseases. But there had been so many false alarms and disappointments with other treatments in the past that it was clear that formal clinical trials were needed to assess these new drugs.

At the time, most clinical trials relied on comparing morbidity or mortality in current patients treated with a new treatment with that in apparently similar, past patients – 'historical controls' – who had either received another treatment, or no treatment.

Comparisons of current patients given new treatments with 'historical controls' can yield trustworthy results when the differential effects of the two treatments are dramatic.[1] But it began to be recognized during the 1930s that such comparisons were not a reliable indicator of moderate treatment effects and differences. In these circumstances, deliberate steps were needed to ensure that the patients in treatment comparison groups were similar, so that 'like would be compared with like'.

Reflecting a growing understanding of this principle, a growing number of clinical trials reported during the 1930s and 1940s used alternation or random allocation of patients to treatment comparison groups, with the objective of ensuring that 'like would be compared with like'. The history of research on the sulphonamides during the 1930s and 1940s neatly illustrates the need for these different kinds of clinical trials. Studies using historical controls were sufficient to provide convincing evidence that sulphonamides had a dramatic effect on mortality from puerperal fever[2–4] and meningococcal meningitis.[5] More carefully controlled trials, using alternation of patients to treatment and control groups, showed that these new drugs also had worthwhile effects on erysipelas,[6,7] pneumonia[8–10] and plague.[11] However, studies using alternation also suggested that sulphonamides were unlikely to be useful for scarlet fever[12,13] and some gastrointestinal disorders.[14,15] In brief, the design of fair tests of the effects of sulphonamides depended on how large an effect, if any, these drugs had on each of the diseases for which they were considered.

When the role of bacteria in infective diseases had become firmly established in the late nineteenth century there were, broadly speaking, two approaches to treatment. The first, and by far the largest, was a series of attempts to attack bacteria by techniques of passive or active immunization, and many of the earliest trials using alternation to generate comparison groups were done to assess the effects of such immunization.[16–21] Passive immunization consisted of injecting a patient suffering from a bacterial disease with serum from an animal (most often a horse) which had been given a series of injections of the bacterium in question to provoke the production of antibodies. The horse was, in effect, used as a factory for making antibodies which were given to the patient as injections of horse serum. The major snag of such passive immunization was that horse serum was apt to produce dangerous anaphylactic reactions, known at the time as 'serum sickness'.

Active immunization consisted of injecting the patient with bacteria which had been attenuated in such a way that they retained their ability to provoke antibody formation, but were too weak to provoke illness. Here, there was no danger of serum sickness, but it takes a considerable time for the body to produce antibodies. Active immunization of healthy people is therefore an effective way of preventing a disease, but an ineffective form of treatment since the patient may die before active immunization has had time to produce immunity.

Immunotherapy dominated the treatment of infective disease during the first thirty years of the twentieth century, but another and totally

different approach was being developed simultaneously. It was an approach which became known as chemotherapy – a term which was first used by one of its greatest proponents, Paul Ehrlich (1854–1915). Although Ehrlich had begun his research with antitoxins, he soon developed a line of reasoning which went something like this: it was known that dyes could be used to stain bacteria on a microscope slide; if dyes could stain bacteria in the laboratory, there might be dyes which could be administered as drugs and stick to bacteria in the human body, killing the bacteria in the process but doing no harm to the patient. Such a drug would, Ehrlich suggested, resemble a 'magic bullet'. Ehrlich had limited success in his search for a magic bullet, but his reasoning explains what at the time seemed very odd indeed – that there might be a link between bacteriology and dyes which were manufactured for the purpose of colouring fabrics and clothing.

The discovery of sulphonamides

This brings us to the work of the German scientist Gerhard Domagk (1895–1964), who discovered the sulphonamides in December 1932. His work, incidentally, brought him a Nobel Prize in 1939, but the Nazi regime refused to allow him to accept it. Fortunately, however, he was able to travel to Sweden after the war to accept the award, but because of the lapse in time he did not receive the financial part of the prize. Domagk was also delighted to be elected to a Fellowship of the Royal Society of England.

When Domagk made his discovery, he was working for the well-known firm of Bayer, which had been founded in 1863 to produce a series of brilliant aniline dyes from coal-tar, a by-product of the coal-gas industry. In 1890, in response to a request to see if they could produce a pain-killing drug, Bayer discovered aspirin. This was so successful that Bayer decided to develop a pharmaceutical division as well continuing to produce dyes.

Domagk, who had served in the German army medical corps in World War I, graduated in medicine after the war and chose research. In 1927 he was appointed Director of Bayer's newly established Institute of Experimental Pathology and Bacteriology. Because Domagk was a great admirer of Ehrlich, he fastened onto the idea that a dye might be the 'magic bullet'. So he arranged that whenever the chemists at Bayer produced a new dye, a sample would be given to Domagk to see if it possessed anti-bacterial activities.
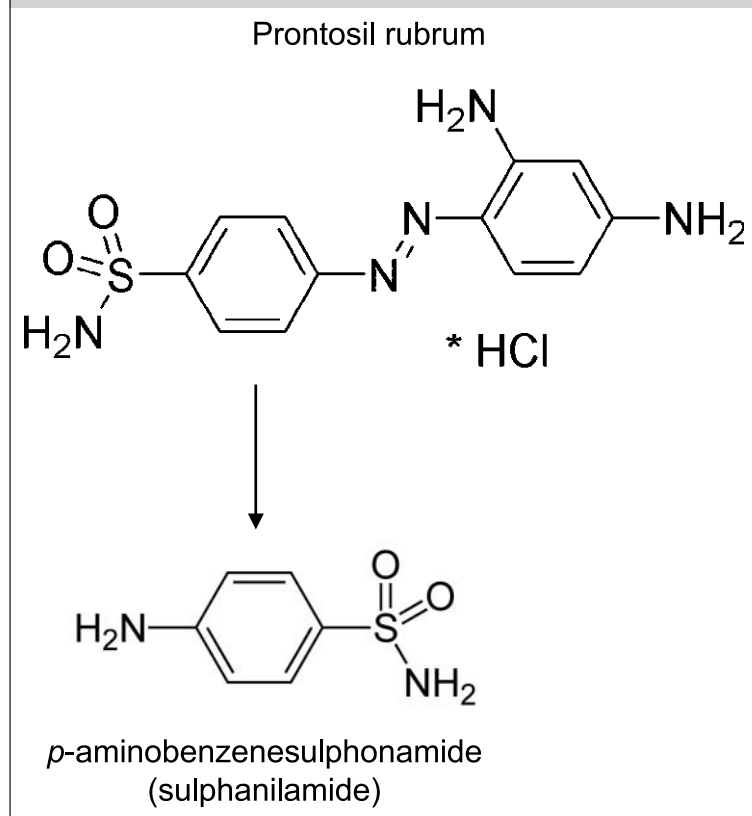
Domagk's established routine was to begin by testing the effect of each new dye on streptococci in vitro in the laboratory. If the dye appeared to attack the bacteria on the plate, he tested the effect on mice. There were many failures until, in December 1932, two of Domagk's colleagues brought along a new red dye which happened to contain a sulphonamide group for the chemically logical reason that it improved the colourfastness in fabrics.

Following his usual routine, Domagk tested this dye in vitro and it appeared to have no effect. Then, for reasons which, as far as I know, he never explained, he departed from his usual routine and tested this new red dye on mice. He took twenty-six mice and injected all of them with a dose of virulent streptococci. Fourteen were kept as controls and twelve were treated an hour and a half after the streptococcal injection with a single dose of the new red dye, administered by stomach tube. The fourteen control mice died within four days; all the mice which had received the red dye survived. The red dye was called Prontosil Rubrum.[22]

This was such an astonishing result that Bayer realized there was a potential fortune to be made. It is still not clear why Domagk did not publish his work until 1935, but it was probably for reasons of secrecy connected with patenting. There were, however, a few reports of using the drug in Germany, but they were not convincing and it is not stated what diseases they treated.[23] But news of this new and supposedly anti-bacterial drug leaked out. At the Pasteur Institute in Paris, Tréfouel and his colleagues asked Bayer if they could have some Prontosil but the request was refused. Nevertheless the scientists at the Pasteur Institute managed to synthesize Prontosil (or something very close to it) and they soon surprised everybody by suggesting that the Prontosil molecule consisted of two parts, joined by a double bond, which was broken down in the body. One part, tri-amino-benzene, produced the red colour but had no therapeutic value, while the other, p-aminobenzene sulphonamide (subsequently known as sulphanilamide), was probably the active anti-bacterial agent. Time proved that the French were right.

This all sounds rather arcane but it was immensely important; for it so happened that sulphanilamide – the active part of Prontosil – had been synthesized in 1908 by a chemist as work for his doctoral thesis. It was not thought to be a chemical of any importance, but its structure had been published (Figure 1). This meant that sulphanilamide could not be patented in the 1930s by

Figure 1
The chemical structure of prontosil rubrum and sulphanilamide

Prontosil rubrum

* HCl

p-aminobenzenesulphonamide
(sulphanilamide)

Puerperal fever is an infection of the genital tract after childbirth. The case fatality rate of puerperal fever varied from time to time but was generally in the region of 20% in sporadic cases. In epidemics, which were common in the eighteenth and nineteenth centuries, fatality rates were much higher. Almost all the serious and fatal cases were due to *Streptococcus pyogenes* (the beta-haemolytic Streptococcus, Lancefield group A). Death was usually due to agonizing generalized peritonitis, or to septicaemia, or both.[22,24] In most cases the source of the infection was the birth-attendant (doctor or midwife) or a member of the patient's family, who happened to be asymptomatic carriers of virulent strains of the Streptococcus.[25]

In the 1920s and early 1930s experimental thera-peutics in Britain was dominated by the influence of Sir Almroth Wright, who was dogmatically certain that the future lay in producing vaccines, and equally certain that talk about magic bullets was pure poppycock. Colebrook and Almroth Wright were temperamentally complete oppo-sites. Wright, who was dogmatic, egotistical and quarrelsome, was totally scornful of any kind of statistical approach. He believed that medical research consisted of thinking about a problem, producing a theory, and then devising one simple experiment to show that the theory was right. Colebrook, on the other hand, was quiet, gentle, humane, self-effacing, cautious and modest to a fault. Yet the odd thing is that, as sometimes happens with complete opposites, they got on very well together.

Influenced by Almroth Wright's faith in vac-cines, Colebrook tried to produce a vaccine against the Streptococcus. Unfortunately there were numerous strains of *S. pyogenes*, and vaccines were strain-specific, which made it impossible to pro-duce a single effective vaccine. Next, remembering that Ehrlich had found that certain arsenicals (the most famous being arsphenamine or 'com-pound 606') could cure syphilis, Colebrook attempted to treat puerperal fever by intravenous arsenicals. But this proved to be so ineffective and so dangerous that it was soon abandoned.

In 1930, Colebrook was appointed Director of the Medical Research Council's research labora-tories at Queen Charlotte's Hospital, a famous London maternity hospital founded in the eight-eenth century. This research unit had been set up specifically for research into puerperal fever. At first, Colebrook concentrated on improving the standard of antisepsis and asepsis, which was sur-prisingly low at Queen Charlotte's Hospital when he took up his appointment, and he remarked

Bayer or anyone else. Moreover, sulphanilamide was much easier and cheaper to manufacture in bulk than Prontosil. Very soon a series of drug firms produced sulphanilamide and marketed it under their own trade name. This brings us to Britain and Leonard Colebrook (1883–1967).

Detecting the effects of sulphonamides in puerperal fever in the UK: convincing evidence using historical controls

Colebrook graduated in medicine at St Mary's Hospital in London in 1906. A year later he joined Alexander Fleming to undertake research in Almroth Wright's department. In 1919 he was appointed as a member of the scientific staff of the Medical Research Council and continued to work at St Mary's Hospital. In the 1920s, motivated by the despair of a friend whose wife had died of puerperal fever, Colebrook changed direction and started to search for a cure of this dreadful disease which was, as it had been for centuries, the greatest problem in obstetrics.

on this at a lecture he gave at the College of Obstetricians and Gynaecologists.[26]

It was only by chance that Colebrook saw a reference to Domagk's work in 1935. With considerable difficulty he managed to persuade Bayer to send him some Prontosil.[27] At this time there were two forms of Prontosil: the original form, Prontosil red, which was insoluble and had to be given by mouth, and a colourless form called Prontosil soluble, which could be given by injection. Later there was another form, Prontosil album, which was closely related to Prontosil soluble.

This marked the beginning of the experimental use of the sulphonamides in the treatment of puerperal fever, which led to the publication of five papers. Four were published in the *Lancet* in 1936 and 1937, and the fifth was published in the *British Medical Journal* in 1937. The importance of these five papers cannot be exaggerated.

The first paper of the four, published in the *Lancet* of 6 June 1936, was not by Colebrook. It described the results of experiments using mice carried out at the Wellcome Physiological Laboratories.[28] This showed that Prontosil and sulphanilamide reduced the mortality of mice that had been injected with *S. pyogenes*. The results were not as clear-cut as Domagk's original experiment, but they were very encouraging.

The second paper, published in the same number of the *Lancet*, was by Leonard Colebrook and Meave Kenny (the resident medical officer at Queen Charlotte's Hospital).[2] It began with a similar experiment with mice, and then described the results of treating patients with puerperal fever. Most of this first group of patients were treated with both Prontosil red by mouth and soluble Prontosil by injection. Behind the formality of a scientific paper, you can detect the excitement of the results. The first patient, who was admitted with a temperature of 104°F, would almost certainly have died without treatment. She was given Prontosil in the evening and 'The team was in and out of the ward all night in the oddest assortment of nightwear'. The next morning the patient's temperature was normal and she recovered rapidly.[27]

At first, Colebrook and Kenny treated only the more severe cases of puerperal fever (10 in number). Later, Colebrook's team treated all cases of puerperal fever due to the haemolytic streptococcus. Thirty eight cases were treated with Prontosil and there were three deaths, giving a fatality rate of 8%. In the 38 cases admitted to Queen Charlotte's Hospital immediately before Prontosil was available, there were 10 deaths, a fatality rate of 26.3%. In the 38 cases immediately before these there were nine deaths, a fatality rate of 23.7%. During the four years 1931–34, the rate varied between 18 and 29%. Colebrook was, however, very cautious:

> 'It behoves us to be very cautious in drawing conclusions as to the curative effect of any remedy upon puerperal infections such as those due to the haemolytic streptococcus in which the exact significance of signs and symptoms is notoriously difficult to assess with accuracy, and in which the prognosis is correspondingly difficult to estimate.'[2]

Colebrook decided that the trial must be extended. He wrote a letter which was published in the *Lancet* of 20 June 1936[29] asking for cases of puerperal fever admitted to other London hospitals to be transferred to Queen Charlotte's. This led to the third paper, which described the results of a further trial of Prontosil in puerperal fever. It was published in the *Lancet* of 6 December 1936.[3] Twenty six consecutive cases had been studied and none had died. Colebrook stressed that some were mild cases who would probably have recovered without special treatment, but there were 14 severe cases, most of whom had positive blood cultures, who would almost certainly have died in the past.

Two of the most severe cases had general peritonitis and also severe septicaemia. Colebrook remarked that, 'This combination has almost invariably proved fatal', but both recovered quickly. Out of the total of 64 cases who received Prontosil, eight had died, giving a fatality rate of 4.7%. This compared with 19 deaths out of the 76 cases (25%) treated before the introduction of Prontosil. Of the eight deaths in the first part of the trial, some were admitted very late in the disease and others were suffering not only from puerperal fever but also from some other unrelated condition which was the probable cause of death.

The fourth paper in this series was published in the *Lancet* in December 1937.[4] The purpose of this study was to see if sulphanilamde was more or less effective in the treatment of puerperal fever due to the haemolytic streptococcus than Prontosil. The total number of patients in this trial was 106, of whom 100 were due to the haemolytic streptococcus. Of these 100, eight died, mostly for unrelated reasons. It seemed that sulphanilamide and Prontosil were equally effective. This was of great practical importance, because sulphanilamide became available on prescription to general practitioners and hospital staff in 1937.

The atmosphere of excitement that greeted the introduction of a highly effective anti-bacterial drug was caught by a leading article in the *Lancet* of 6 June 1936, which also carried the first two papers:

'The history of attempted chemotherapy in bacterial infections is so discouraging that any indisputable success in this direction is almost totally unexpected. It has seemed hitherto that some radical difference between protozoal and bacterial infections offers an insuperable bar to the treatment of the latter by chemical means. Nothing in therapeutics is more certain than the disappearance of malarial parasites or trypanosomes under the influence of appropriate drugs; nothing has been more uncertain or perhaps more frankly disappointing than the effect on such a condition as streptococcal septicaemia of administering all kinds of supposedly bactericidal compounds… The conclusions drawn by Drs Colebrook and Kenny on the basis of their clinical experience are commendably cautious. It is very much hoped that the therapeutic trial which they have initiated in this country will be extended to embrace types of streptococcal infection other than puerperal fever.' [30]

Many researchers would have been content with the results of first trial based on 38 cases. But Colebrook was cautious to a fault. His main worry was that the fall in mortality might have been due to a decline in the virulence of the streptococcus. He made inquiries of other hospitals and found that in some, but not all, there was evidence of a decline in virulence, but it was deemed insufficient to explain the fall in mortality. What seems to have convinced Colebrook more than anything else was the promptness of the recovery of several patients who were so ill that they would previously almost certainly have died. Colebrook was also anxious about side effects from the sulphonamides (some of the patients were cyanosed) but these were shown not to be serious.

In October 1937, before Colebrook and Purdie had completed their third trial and reported it to the Therapeutic Trials Committee of the Medical Research Council, the fifth paper, written by Gibberd, was a commentary on Colebrook's research.[31] Frank Gibberd was, at that time, assistant surgeon to Guy's Hospital and Obstetric Surgeon to In-patients at Queen Charlotte's Hospital. He published the paper with the blessing of Colebrook and his team. I suspect Colebrook was happy to have his work reviewed by someone outside the Medical Research Council Unit, and

also by the publication of this review in the *British Medical Journal*, which had a wider readership than the *Lancet*. The results of Colebrook's trials were set out with great clarity on the first page of Gibberd's paper.

It certainly seemed beyond doubt that in severe cases of puerperal fever – especially cases in which there was severe septicaemia or peritonitis or both (line *d* in Table 1) – Prontosil and sulphanilamide were highly effective, not only because they reduced the mortality rate by a very large amount, but also because recovery was so prompt. The single case of a woman who had both septicaemia and peritonitis but died in spite of receiving Prontosil (line f in Table 1) died from pulmonary embolus.

Nevertheless, Gibberd took the possibility that the fall in puerperal fever mortality might have been due to a fall in the virulence of the streptococcus very seriously indeed. He cited a London hospital at which no sulphonamides were used in which the mortality from puerperal fever had been falling over several years, but it was a prolonged and relatively slight fall. In the end he thought it extremely unlikely that the results achieved by Colebrook were due to a fall in streptococcal virulence which just happened to coincide with the introduction of the sulphonamides; but he stressed that this was a real, if remote, possibility and further trials should be carried out. They were, and the effectiveness of the sulphonamides in the treatment of streptococcal puerperal fever was shown by studies reported from Glasgow,[32] Edinburgh[33] and Belfast,[31] in all of which historical controls were used.

Just how quickly the sulphonamides became known is shown by the story of a general practitioner in a small market town in Gloucestershire which had a maternity unit in the local cottage hospital. Maternity patients were confined to the hospital for several days post-partum in case they developed puerperal fever. When a case of puerperal fever did occur, this general practitioner knew from bitter experience that 'you could do precious little but pray'.

While reading the *British Medical Journal* over breakfast in the summer of 1936, this general practitioner, who happened at the time to have a case of puerperal fever in the local hospital, saw a report from a London hospital of a dye which appeared to have antibacterial properties. He picked up the telephone and managed to contact the author of the report, demanded a sample of his dye to use on his patient, and suggested that if it was put on the noon train from Paddington station he would meet

Table 1
Results of puerperal infections due to the haemolytic streptococcus. Adapted from Table 1 in Gibberd[31]

	1934–35 group			1936–37 group		
	Cases (n)	Deaths	Mortality (%)	Cases (n)	Deaths	Mortality (%)
(a) Total number of puerperal infections due to the haemolytic streptococcus	210	42	20	157	7	4.5
(b) Total number of infections clinically limited to the birth canal	98	0	Nil	104	0	Nil
(c) Total number of infections showing definite clinical evidence of localized spread beyond the limits of the birth canal (excluding cases with septicaemia)	50	0	Nil	30	1	3.3
(d) Total number of infections in which the haemolytic streptococcus was demonstrated on blood culture (excluding cases in which generalized peritonitis was also proved)	28	11	40	21	5	20
(e) Total number of infections in which generalized peritonitis was proved to be present (excluding septicaemia)	18	15	83	1	0	Nil
(f) Total number of infections in which both septicaemia and generalized peritonitis were proved to be present	16	16	100	1	1	100

the train personally. Not expecting any response he met the train and the guard handed him a neatly wrapped brown paper parcel in which there was a vial of crystals without any instructions. He divided the crystals into three, and dissolved each third part of the total in sterile water. By this time his patient was almost comatose with a high fever. She was given the injections, the fever promptly receded, the patient recovered and was still alive and healthy in the 1970s.[22] A survey carried out in December 1937 showed that the sulphonamides were already being widely used in general practice.[34]

Detecting the effects of other uses of sulphonamides: the need for unbiased concurrent comparison groups

Should Colebrook have investigated the effects of sulphonamides using a trial with concurrent controls who did not receive chemotherapy? To have done so would have removed the anxiety about the possible decline in streptococcal virulence, which worried Gibberd even more than Colebrook. But puerperal fever was an exceptionally tragic and acute disease with a high fatality rate. Colebrook was so impressed (and rightly so) by the rapid recovery of patients[3] with severe septicaemia and

generalized peritonitis – cases which had almost always died before 1936 – that I doubt if it had ever entered his mind to do a clinical trial using untreated concurrent controls. It would have been unethical, for it would have meant withholding either Prontosil or sulphanilamide from some of these exceptionally severe cases and watching them die. That would have been unthinkable, then or now. A similar judgement would be appropriate in respect of the use of sulphonamides in cerebrospinal fever (meningococcal meningitis, often known at the time as 'spotted fever'), where the new drugs also achieved dramatic reductions in mortality.[35]

However, the effects of sulphonamides in other diseases – erysipelas, pneumonia, measles, scarlet fever and gastrointestinal infections – in which the majority of patients survived, could not so easily be inferred without more carefully controlled trials. Because the effects of the drugs were likely to be less dramatic, historical controls might well be misleading because of biases resulting from differences between the comparison groups other than use of sulphonamides. In these circumstances, it was necessary to assemble concurrent comparison groups prospectively using a method – alternation or randomization – which would help to ensure that like would be compared with like. A number of such trials were conducted in the late 1930s and early 1940s.

Two controlled trials conducted in Glasgow (supported by the Medical Research Council) compared sulphonamides with ultraviolet light in erysipelas (infection of the subcutaneous tissues). The first of these assessed Prontosil,[6] the second sulphanilamide.[7] Patients were allocated to the comparison groups by rotation, in the order they were admitted to hospital, and the authors note that this achieved groups that were very similar in respect of factors known to be important in the prognosis of the condition. Deaths associated with erysipelas were rare and no conclusion was possible on the effects of sulphonamides on mortality. However, the trials did show a beneficial effect of the drugs on the duration of spread of the lesion, pyrexia, and 'toxaemia' ('prostration, headache, state of tongue, insomnia, vomiting abdominal distension, and delirium').

Similar findings were obtained in controlled trials of sulphapyridine in pneumonia:[8,10] effects on pyrexia and rate of recovery were demonstrated, but no confident conclusion could be reached about the effects on mortality associated with the disease. Another controlled trial done in Glasgow with support from the Medical Research Council assessed the effects of giving sulphanilamide to children with measles in an effort to prevent the bacterial infections that can complicate that viral disease. Again, although no effect on death was detected, the drug reduced the incidence and duration of pneumonia, and the results suggested that it might also reduce otitis media. In addition to helping to quantify the less dramatic effects of sulphonamides, these controlled trials using concurrent controls began to quantify the adverse effects of the drugs (cyanosis and gastrointestinal problems, for example).

Trials using concurrent control groups also helped to identify the circumstances in which sulphonamides seemed unlikely to be useful. There were at least two controlled trials of sulphanilamide in scarlet fever,[12,13] neither of which detected any beneficial effect of the drug on this disease, in spite of the fact that it was caused by *S. pyogenes*. The author of the first of these studies, JC Hogarth, suggested that a combination of three factors might have been important. First, the disease might have become too mild for an effect to be detected (the fatality rate of scarlet fever had been declining steadily from the late nineteenth century, while the fatality rates of puerperal fever and erysipelas had not declined significantly since the nineteenth century[22]). Other possible explanations suggested by Hogarth were that the causative organism might be a strain of streptococcus

that was insensitive to sulphonamides, or that sulphanilamide might be less active than Prontosil. Whatever the explanation of the ineffectiveness of the sulphonamides in scarlet fever, it is salutary to realize that if the first trials of the sulphonamides in streptococcal disease had been carried out only on cases of scarlet fever, these drugs might have been dismissed as of no importance. Similarly disappointing results were obtained in controlled trials of sulphonamides in gastrointestinal infections.[14,15]

Conclusions

We have now become so familiar with the wide range of antimicrobial drugs that it is difficult to imagine how important, how revolutionary, the sulphonamides seemed to be in the 1930s and early 1940s. An unsigned leading article in the journal *Public Health* in October 1943 gives us a picture of the great importance attached to the sulphonamides at a time shortly before penicillin became generally available. The writer noted that 'puerperal infection with the streptococcus has almost ceased to be a cause of maternal mortality' and that the sulphonamides had been shown to be effective against erysipelas, pneumonias, meningococcal and gonococcal infections, bacillary dysentery and urinary infections. The sulphonamides had reduced mortality of cerebrospinal fever (meningococcal meningitis) from 70 to 20%. Because epidemics of this disease were common at the time, especially amongst adolescents and young adults, the writer thought this was 'where the sulphonamides have, perhaps, had their greatest victory'.[35] By the time this editorial was written, not only were many drug firms producing sulfanilamide under their own brand names, but some were synthesizing new types of sulphonamide. In spite of the dramatic effects of sulphonamides which were identified with confidence using historical controls, when the new drugs were used in some conditions, more carefully controlled trials were needed to distinguish between circumstances in which they had more modest effects and circumstances in which they seemed very unlikely to be of use. The controlled trials also began to identify and quantify the side effects of the new drugs.

When penicillin became available, the publicity was so enormous that the sulphonamides were pushed to the back of the stage. Penicillin did indeed have one advantage in the treatment of puerperal fever: unlike the sulphonamides, penicillin was not only highly effective against

streptococcal puerperal fever but also against *Staphylococcus aureus*, which caused between 4 and 5% of deaths from puerperal fever. But that does not detract from the success of the sulphonamides. In England and Wales in 1934, just before the introduction of the sulphonamides, the maternal mortality rate due to puerperal fever was 19.5 per 10,000 births: and it had remained at about this level since the mid-nineteenth century. After the sulphonamides were introduced the mortality rate dropped to 5.4 in 1940 and to less than three by 1944, when penicillin started to become available.[24] The fact that the sulphonamides had saved thousands of lives before penicillin was introduced was the greatest tribute to Domagk's discovery of the antibacterial properties of Prontosil in 1932. Moreover, Ronald Hare, who was involved in the introduction of penicillin, remarked in 1970: 'Let there be no doubt about it, without the sulphonamides to show the way, it is improbable that penicillin would have emerged from its obscurity'.[36]

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