MEDICAL PRACTICE

In My Own Time

The eclipse of the haemolytic streptococcus

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British Medical Journal, 1979, **1**, 1607-1608

My first encounter with acute septic infection was at the 1st Eastern General Military Hospital, Cambridge, where I worked for some time in 1916 as a dresser, assistant anaesthetist, and assistant in the pathology department between passing 2nd MB and entering the Navy as a surgeon sub-lieutenant. This was a hutted hospital on what had been the cricket ground of my college (now the site of the university library) with 2000 beds mainly occupied by battle casualties from France, who reached us by direct hospital train from the channel ports. Although transit time from the front line was usually not more than 24 hours, gas gangrene had sometimes developed by the time of admission, and even when amputation was feasible I cannot recollect a single survival. Later deaths from sepsis must often have been due largely to streptococcal infection, but the laboratory was much too small to make any regular study of wound flora.

Damaging the invaders

It was here that something happened which has deeply influenced my thinking ever since. I was assisting the pathologist, Captain D Mallam, RAMC(T), at a necropsy on a man who had died with, and probably of, wound sepsis, when he punctured a finger on the sharp point of a fractured bone. This type of trivial injury, as I shall later have occasion to explain, is exceedingly dangerous. He removed his glove, dipped a matchstick in pure liquid phenol, pressed this firmly on the point of puncture, and maintained this pressure for what seemed a very long time, then donned another glove, finished his work, and later was none the worse for what had happened. What he had achieved was a painless (since phenol is also a local anaesthetic) chemical necrosis of the entire small area which had been contaminated, and total destruction of the contaminants.

It was at this time that Almroth Wright was engaged in bitter controversy with Army surgeons about the use of antiseptics in wounds, maintaining that they did far more harm than good (as indeed, as sometimes used in France, they probably did). For many years after this he and his colleagues at St Mary's, including Fleming, continued to preach the same doctrine, despite improvements in antiseptics and methods of their use, illustrating their argument by endless slide-cell experiments showing that leucocytes were much more easily killed by antiseptics than bacteria. I have never been entirely convinced by this argument; what does it matter if a few leucocytes are killed initially when there are limitless reserves of them to draw on, provided that at the same time the invaders have been severely damaged? But at least the opponents of antiseptics should admit that if it is possible by their use *completely to disinfect* a wound (as in the exceptional instance I have described), it is ungrateful to complain of a little local damage to tissues. There is now another way of preventing infection from punctured wounds, so often cited as illustrating the futility of local applications. German workers on the acridine antiseptics showed that they would prevent streptococcal infection not only in incised wounds but also—when the area was later infiltrated with a solution of the antiseptic—in subcutaneous tissue infected by injection.

Haemolytic streptococci are the most versatile of all bacteria. At the end of the 1914-18 war they made a large contribution to the huge mortality from the influenza pandemic. In fatal cases there was a secondary bacterial pneumonia often due, at least in part, to these streptococci; my recollection is that if an empyema developed, they alone were found in it. It is interesting that in more recent times fatal pneumonia complicating influenza has often been staphylococcal. Haemolytic streptococci are also

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responsible for two specific infections—erysipelas and scarlet fever. The severity of scarlet fever, which once had a considerable mortality, has steadily diminished throughout most of this century, but mortality from infection at other sites—now to be considered—did not follow this trend.

The worst manifestation of streptococcal infection has always been puerperal fever, worst in the sense that a young woman in perfect health, fresh from the supreme experience of bringing a new life into the world, could herself within a few days be taken from it. The scale of this mortality has not in modern times approached that against which Semmelweis fought his uphill battle, but in England and Wales in the twenties and early thirties deaths from this cause—most fatal infections being streptococcal—numbered about 1000 per annum, despite modern knowledge of bacteriology and hygiene and strenuous efforts directed towards both prevention and cure.

Fatal pricks and scratches

One special type of the infection, which also claimed victims in the prime of life who could ill be spared, was seen in medical personnel. Most large hospitals have records of tragic deaths from this cause. At my own, the youngest surgeon on the senior staff, an athlete with an unexampled record as a Cambridge rowing blue, died from it in 1913, and in my own time two surgical registrars. Nurses and pathologists have also not been exempt. In each of the two cases of which I have personal knowledge, infection was through a finger prick or scratch during attendance on a septic patient, and such was the almost invariable history. There was an acute cellulitis of rapid onset, spreading to the arm, and outpaced by the clearly visible red lines of an ascending lymphangitis; the onset of septicaemia was heralded by high fever and rigors. Meanwhile, the patient from whom the infection was derived had not always been so acutely ill, and indeed sometimes recovered. How is this paradox to be explained?

The virulence of all bacteria, which may loosely be defined as their capacity to produce disease, is affected by their past environment. In prolonged artificial culture it diminishes, and in the end may be almost entirely lost, as, for instance, in BCG. In the animal host it is retained, and is also enhanced by transfer from one host to another—a process known in the jargon of bacteriology as *passage* (French pronunciation). This change is more rapid and extreme in the haemolytic streptococcus than in any other species. An old laboratory culture may fail to kill a mouse unless a dose of perhaps 10^8 organisms is used. Washings from its peritoneum will infect another mouse in a dose of perhaps 10^5. If *passage* is continued, a point is soon reached at which fatal infection results from an inoculum so dilute as to yield only about three or four colonies in culture ("colony-forming units," as they are called, are in this species not single cocci but chains). Thus in a series of hosts successively infected at short intervals, virulence may be enhanced by something like tenfold at each transfer. Hence the devastating effect of the small inoculum in these trivial surgical accidents.

A remedy discovered

The outlook was utterly transformed in 1935 by what, in my view, was the outstanding therapeutic discovery of modern times. The successors of Ehrlich in Germany—imbued, like him, with the belief that the strong affinity of aniline dyes for bacterial protoplasm could be turned to such account—continued to test long series of dye compounds for their capacity to protect mice against infection, and eventually struck a winner in sulphamido-chrysoidin (Prontosil). This drug protected mice against a lethal inoculum of haemolytic streptococci, and clinical confirmation of its action in erysipelas and other infections was quietly obtained before full announcement of the discovery was made early in 1935 by Domagk in Germany and by Hörlein at a meeting at the Royal Society of Medicine in London. I was present at this meeting and was fully convinced by the claims made, but neither I nor I am sure anyone else who was there foresaw what was to follow.

Within a few months the Tréfouels in Paris had shown that Prontosil is split in the body into two components: chrysoidin, the dye, which is therapeutically inert; and *p*-aminobenzenesulphonamide (later known as sulphanilamide), a substance with an antistreptococcal action demonstrable in vitro (Prontosil had none), to which therapeutic effect was undoubtedly due. This was a double blow to the Germans: to their pride, because their belief both in dyes and in the necessarily mysterious action of *echt Chemotherapeutika* was discredited; and to their pockets, because sulphanilamide had been described many years earlier and so could not be patented (it was soon being made by enterprising drug firms everywhere and marketed under about 70 different names). Prontosil, apparently an all-time winner, became within a year a back number. At the same time, a wide extension of the scope of this treatment became possible. Sulphanilamide proved to be effective in cerebrospinal fever, gonorrhoea, gas gangrene, and some coliform infections, and further compounds derived from it provided remedies for other infections, notably pneumonia.

In Britain the earliest systematic investigator of the action of Prontosil, and later of sulphanilamide, was the late Leonard Colebrook, who was well placed in the isolation department at Queen Charlotte's to undertake such a study. Mortality from puerperal fever fell immediately and steeply. Ten years later penicillin took over this task—another great mercy since, by then, some strains of streptococci were becoming sulphonamide-resistant. We should be profoundly thankful that resistance to penicillin, at least in streptococci of group A, has never developed and probably never will. Streptococcal puerperal fever is now an almost unheard-of cause of death, possible only as the result of misdiagnosis or mismanagement. The same is true of other forms of infection described here; any acute local infection can so easily be arrested that the stage of septicaemia need never be reached.

Those without long memories may not agree that here was "the outstanding therapeutic advance of modern times." The reduction in mortality from pneumonia, tuberculosis, and typhus has doubtless been greater. But this was the first bacterial (as distinct from protozoal) infection to become amenable to chemotherapy, and in the quality of some of the lives lost by it, and in the circumstances of such loss, old-fashioned haemolytic streptococcal infection stands in a class apart.

Patients with extensive psoriasis sometimes show fatty changes in the liver, the significance of which is uncertain. Might these liver changes be a toxic effect of long-term application of ointments containing salicylic acid or tar to large areas of affected skin?

Minimal changes have been found in the livers of patients with extensive psoriasis and eczema. These changes are not usually associated with abnormalities of hepatic function, and while they are generally thought to be secondary to the rash rather than to its treatment there has been little recent work on this subject, which is in urgent need of reinvestigation.

Shuster, S, and Marks, J M, *Systemic Effects of Skin Disease*. London, Heinemann, 1970.

Is impotence a recognised side effect of indomethacin suppositories?

I cannot find any reports of impotence associated with the use of indomethacin—either as suppositories or taken by mouth; and the manufacturers of Indocid are not aware of any reports. Furthermore, impotence is not a recognised side effect of any of the other non-steroid anti-inflammatory analgesics. Loss of libido has been occasionally reported, which is not surprising because indomethacin not uncommonly produces central side effects including depression.