Tribute to Ogston's Coccus: a paradigm of the modern carrier problem

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It is a great privilege to be invited to deliver the first Ledingham Lecture, a privilege greatly enriched by the fact that it is to be delivered at the celebration of the centenary of Ogston's description of my favourite bacterial species.

John Charles Grant Ledingham was born just five years before Ogston described his coccus, in 1875. He had a remarkable academic career in the University of Aberdeen which he entered in 1891 and where he distinguished himself both in classics and science, graduating MA in 1895 with first class honours in mathematics and natural philosophy. Having in 1897 decided to study medicine, he won a gold medal in anatomy, took a B Sc in mathematics, physics, anatomy and anthropology, and graduated MB, Ch B, in 1902. In 1904 Ledingham migrated to London and in 1905 joined the staff of the Lister Institute of Preventive Medicine, where he was to remain for the rest of his working life, being Director from 1931 to 1943. Ledingham was elected a Fellow of the Royal Society in 1921 and was knighted in 1937. He died in 1944, only one year after his retirement from the Lister.

Ledingham's obituary in the *Journal of Pathology and Bacteriology* lists over 120 publications. In his earlier years he was concerned particularly with the mechanisms of phagocytosis and with the bacteriological and epidemiological problems of carriers of typhoid bacilli. Later his interest switched to viruses with particular attention to the pox viruses; he was also an energetic advocate of a more vigorous immunization policy against various virus infections.

Ledingham's contribution to the book, published with Arkwright in 1912, *The Carrier Problem in Infectious Diseases*, dealt principally with the enteric fevers and in particular with the great efforts being made in Germany, during the first decade of this century, to control typhoid fever by active pursuit of healthy carriers.

The first J. C. G. Ledingham Lecture.

Ledingham did not, so far as I can detect, ever concern himself with the staphylococcus, which seems to provide a good example of a carrier problem quite different from that studied by Ledingham and his colleagues but, in our time, just as important as typhoid was in his. Ogston's coccus has continued as a cause of wound sepsis, of skin infection in neonates and adolescents, and of septicaemia, through to the present, and it has, particularly in the last 40 years, provided a source of intellectual stimulus and argument and, in consequence, surely of pleasure, to generations of microbiologists. My endeavour in this lecture, therefore, is to offer as my tribute to the memory of Sir John Ledingham, and as a conclusion to this centennial conference, some account of the lessons, many of them linked in one way or another with the carrier problem, that we have learnt from studies of Ogston's coccus.

THE CARRIER STATE

Although healthy carriers of typhoid and diphtheria bacilli had been recognized since early in this century, these were rare in the general population and almost all were thought to be either incubating or convalescent from an acute infection. In the 1930s the work of Colebrook and his colleagues revealed the existence of symptomless carriers of haemolytic streptococci and demonstrated their importance in the epidemiology of puerperal infection. But neither of the first two editions of Topley & Wilson's bible of bacteriology, published in 1929 and 1936, mentions healthy carriers of staphylococci. The reason, surely, must be found partly in a statement appearing in both those editions, to the effect that no classification of staphylococci was then practicable. Dr Hill's account, in this Conference, of the taxonomists' various efforts to classify the staphylococci and micrococci during the first half century after their initial recognition makes it quite clear why so pragmatic a bacteriologist as G. S. Wilson should have been dismissive. As Dr Hill pointed out, the coagulase test was rediscovered in the late 1930s and, once it had been recognized that all staphylococci from septic lesions produced coagulase, it was accepted that this test was an adequate indicator of pathogenicity; it was then practicable to seek healthy carriers of pathogenic staphylococci—of Ogston's coccus. Within a few years there were reports from a number of centres demonstrating nasal carrier frequencies between 20 and about 50 per cent and skin carriage in some 20 per cent of normal adults.

Once initiated, studies of the carrier problem in staphylococci rapidly grew to a spate and revealed that carriage of staphylococci was quite a

different phenomenon from the carrier problem that Ledingham & Arkwright had analysed for the typhoid and diphtheria bacilli (Williams, 1963). Staphylococci that have all the characteristics of pathogens are clearly part of the normal bacterial flora of many healthy people, apparently well adapted to a prolonged peaceful commensal existence. But in appropriate circumstances they can invade the host who has sustained them for years, and produce profound disease. The 'appropriate circumstances' are generally fairly clear: accidental or medical trauma of one sort or another being the most obvious; what is not clear is whether the battery of toxins and the like that seem to be responsible for enabling the cocci to produce disease have some other function in assisting the commensal life, and if not why they continue to be produced.

The fact that, as Professor Oeding pointed out, the carrier state induces an active antibody response makes it quite clear that the staphylococci do produce many of their antigens while in the commensal state.

I think that when this Jekyll-and-Hyde behaviour was first appreciated as characteristic of Ogston's coccus it was regarded as unusual, perhaps unique, among pathogens. No longer. *Escherichia coli,* as a commensal in the gut and a pathogen in urinary tract and blood stream, has a very similar behaviour pattern; likewise, *Clostridium perfringens* living in the gut and producing gas gangrene in amputation stumps, *Streptococcus milleri* living in the gut and producing abscesses in the lung or brain, *Streptococcus mutans* invading the endocardium from its home on the teeth. The pattern first recognized approximately 40 years ago with staphylococci is now seen to be characteristic of a wide variety of bacterial Jekyll-and-Hydes.

The realization that individuals had different characteristic patterns of staphylococcal nasal carriage, some people being very persistent carriers, some persistently non-carriers, some intermittent carriers, and that the patterns of skin carriage are equally variable, naturally posed the question of the origin of the carrier state. There was, in any case, interest round the same time in staphylococcal infections in maternity units, stimulated by the occurrence of a number of epidemics of skin sepsis among the infants and of breast abscess in their mothers. It was soon clear that the picture was quite different from that of the haemolytic streptococcus which staphylococci had largely replaced as the dominant infection of the maternity hospital (Williams *et al.,* 1966); in the maternity nurseries of the 1950s virtually all infants were colonized by *Staphylococcus aureus* within 3 or 4 days of birth. Unfortunately there never seem to have been any adequate studies to determine how neonatal carriage relates to carriage later in life. There is some evidence that the nasal carrier rate is quite low in young children before rising to the adult level in adolescence. It would be

fascinating to know whether the staphylococci of the adult are ever quiet persisters from those that infected the infant.

Adult patients have frequently been shown to acquire nasal carriage of hospital staphylococci—characterized by resistance to antibiotics—at a steady rate during their stay in hospital, well illustrated in Dr Lidwell's contribution. This is of particular importance because nasal carriers seem to be at increased risk of post-operative staphylococcal wound infection, particularly if they have become carriers of hospital staphylococci.

Mr Jellis's paper on staphylococcal infections in the tropics made one realize how little we know of the staphylococcal carrier state in inhabitants of the tropics; one wonders whether the disease peculiar to the tropics could be in any way related to peculiarities in the carrier state.

Type Differentiation

The great prevalence of *S. aureus* in the nose and on the skin of normal healthy people and the evidence from quantitative comparison of wound infection rates in carriers and non-carriers made the need for a typing system evident very soon after the distinction of pathogen from non-pathogen, on the basis of coagulase, was recognized. Cowan was among the first to try a serotyping system but only 3 types could be distinguished. Although Oeding and some others have conducted extensive investigations into the antigens that could be used as a basis for a more satisfactory serotyping test, phage typing is the method that has been used in almost all epidemiological studies. Wilson & Atkinson took up an observation recorded by Fisk to the effect that phages of varying specificity could readily be demonstrated. At that time the system for type identification in *Salmonella typhi* based on Vi-phages had been described by Craigie & Yen. In the *S. typhi* system all the typing phages were developed by 'adaptation' from a single parent and each distinct type was recognized by susceptibility to a single phage. It was soon evident that no such system was practicable for the staphylococcus, and although Wilson & Atkinson tried to devise a system in which a limited number of types were recognized, subsequent work soon showed that this was impracticable (Williams & Rippon, 1952). Ogston's coccus again led the way, for subsequent systems of phage typing for a variety of bacteria have had to rely on differences between patterns of varying complexity. The fact that we were looking for differences between patterns comprising up to 10 or so reactions with the set of 24 phages clearly called for a sort of convention for distinguishing types different from that which is practicable with a set of mutually exclusive reactions, and it

provoked us into some very early attempts at quality control, including the organization from 1955 of international quality control tests.

It was also, I think, Ogston's coccus that provided the first examples of the phenomenon, now widely recognized, of phage-determined phage-type (Asheshov & Rippon, 1959).

As Professor Shooter told us, phage typing enabled us, in the 1950s, to gain a much more detailed picture than would otherwise have been available of the staphylococci that, having acquired resistance to penicillin, streptomycin and tetracycline, were found responsible for major sepsis in surgical wards and minor sepsis (plus breast abscesses) in maternity units. In the 1950s we had a relatively small number of what appeared to be 'epidemic staphylococci', of which one, known as type 80/81, gained such notoriety throughout the world that it seemed to some to be the only staphylococcus that mattered. Professor Shooter has recounted some of the features of the epidemic staphylococci of the 1950s and their subsequent evolution or, perhaps more precisely, the subsequent evolution of the staphylococcal picture. At the present time staphylococci that could, by any criterion, be called 'epidemic' are very rare both here and in the United States, and we have no idea why this should be. These longer-term changes in type distribution are not generally attributable to patterns of antibiotic usage. Some of the changes in phage type are certainly due to the gain or loss of type-determining phages. Presumably the phage genome can sometimes affect not only the type pattern but also those, mostly as yet undetermined, characters of the staphylococcus that determine its communicability and virulence. Professor Arbuthnott has reported clear evidence for the control of one of the epidermolytic toxins by an extracellular plasmid in some strains.

Antibiotic-resistant Infection

The appearance of antibiotic resistant staphylococci in patients under treatment led to argument, assertion and investigation of their origin. Although easy to 'train' to some degree of penicillin-tolerance, penicillinase-producing staphylococci could not be produced by exposure of pure cultures to penicillin in the laboratory. It was concluded that they must have long existed in nature (and indeed some penicillinase-producing strains have been found in pre-penicillin collections) and been selected by the use of the antibiotics.

With the development of bacterial genetics, it became clear that the antibiotic resistance—including penicillinase-production—could be newly

acquired by staphylococci through the transmission, probably generally phage-mediated, of the relevant plasmid (Dyke & Richmond, 1967). So we seem to have elegant variation in the way in which resistant staphylococci can appear—through selection of long-existent natural strains, propagated through the human population by the various modes of transmission summarized under the term 'cross-infection', or by the acquisition of a resistance-determining plasmid, and at least one example has been published where it appeared that phages, which can carry plasmids, were being spread, in epidemic fashion, through a hospital population of staphylococci (Bulow, 1970).

The staphylococcus has offered us, or rather we have offered to the staphylococcus, the opportunity to illustrate very clearly some relation between antibiotic usage and the prevalence of antibiotic resistant strains. One crisp example came from Lowbury's work in the Burns Unit at the Birmingham Accident Hospital, where, in the face of widespread use of neomycin preparations, a neomycin-resistant staphylococcus spread to the extent of infecting 74 per cent of the patients; when neomycin was withdrawn, the resistant strains diminished and ultimately disappeared (Lowbury *et al.,* 1974). There have, of course, also been surprises like the failure of methicillin-resistant staphylococci to spread to any very great extent after their initial appearance in 1961, despite wide use of methicillin and cloxacillin.

The evolution of hospital staphylococci has been discussed in this symposium by Professor Shooter and Professor Altemeier, and it is clear that although some part of the mechanism of the evolutionary changes observed can be attributed to the acquisition or loss of phages, and in some way some of these changes may be aided by the selection pressures of antibiotics, we are really largely ignorant of the factors determining the big changes. Nor do we have much useful information as to what is happening among the staphylococci in the general population outside hospital. Our lack of understanding in this field seems in contrast to some of the other pathogens for which we have at least some glimmerings. In closed populations the changes in serotype of *Streptococcus pyogenes* seem to be explicable on the basis of acquired immunity; the same is presumably also true for the influenza virus, coupled with some mysterious genetic sorting process that has provided a series of variants able, until recently, to circumvent the immune barriers erected as a consequence of the wide spread of a single serotype. In salmonellas, we can recognize a quite different basis for the comings of new serotypes and often for the goings of some old serotypes, namely new sources in new foodstuffs (or new sources of pollution for old foodstuffs). Although staphylococci are widespread in

animals, and animal strains, in some circumstances certainly, have different phage types from those found in man, we do not, I think, have any idea whether there is any interaction between the human and animal staphylococcus populations.

EXPERIMENTAL INFECTION

There is an irresistible temptation, for microbiologists, to believe that experimentation in animals that do not in nature suffer infection by some particular microbe can constitute a valid model for infection by that microbe in man. Dr Easmon has discussed the problem of constructing meaningful models for human infection with staphylococci, and has shown very clearly how the extent to which one can regard a staphylococcus as virulent depends critically on the particular experimental model that is used. Dr Marples has reviewed the history of direct experimentation in man, emphasizing that the early studies were directed mainly at confirming the pathogenic capabilities of the cocci, and later at attempting to resolve the problem as to whether staphylococci or streptococci caused impetigo. Later came the work of Elek, clearly aimed at elucidation of the details of the pathogenic mechanism, in which he used himself and his colleagues in an attempt to determine the minimal infecting dose. But the opportunities for such experiments, never great, have diminished to vanishing point in the current social scene. Dr Marples' own studies, designed to provide tests on man that will satisfy drug regulating authorities, have provided valuable information, but even though the lesions produced are relatively mild the tests could hardly be done on the numbers of volunteers required to yield statistically valid estimates of an ID_{50}, let alone an $ID_{0.05}$ which might well be a more realistic representation of the real-life situation.

The various experimental approaches described by Dr Easmon have shown how much we can learn about the mechanics, immunology and toxicology of staphylococci from experiments in mice. We are left, however, with rather few clear links between the results from experiments in mice, and the disease we see in patients. This is why the work described by Professor Arbuthnott and Dr Lyell on the epidermolytic toxin, which really does seem to be the agent causing the scalded skin syndrome in infants, is so encouraging. Dr Easmon's indication that the peculiar reaction to staphylococci in children with chronic granulomatous disease may be explained on the basis of the delayed hypersensitivity reaction studied in his animal experiments, also gives hope that useful models can be developed.

As an alternative to whole mice or whole men, there have been many attempts to unravel pathogenesis by study of phagocytosis, as described so elegantly by Professor Quie, with the impressive help of a panel of patients (and mice) with rare specific defects in their immunological systems. As so often in medicine, we seem to understand more about the rare diseases and phenomena than about the common. We have now a far clearer picture of the pathogenesis of the staphylococcal epidermolytic toxic syndrome than of the ordinary boil on the back of the neck.

COAGULASE-NEGATIVE STAPHYLOCOCCI

Among the pleasures that microbiologists have derived from Ogston's coccus must surely be the opportunity it has offered for argument on its name, argument that, as Dr Hill has shown, commenced right from the time of the first description of the organism. Dr Hill's contribution demonstrates very clearly the productivity of microbiological taxonomists and how long it took to crystallize a formal classification that was useful to the medical microbiologist. The apparent decline of the obviously epidemic Ogstonian staphylococci in the last decade, coupled with the development of a variety of new surgical and medical procedures, have brought into prominence the non-Ogstonian cocci—what Dr Parker has called shortly the 'other' staphylococci, but which Dr Hill has shown can at the latest count be put into 14 different 'species'.

If we were seeking candidates for the near-ideal 'harmless commensal' most microbiologists would until recently have been prepared to put coagulase-negative staphylococci high on the list. Dr Parker's contribution shows that among the varieties of cocci subsumed under the broad rubric of 'coagulase-negative' there are some that are well equipped to cause disease in certain defined situations and conditions: not so much all-purpose pathogens as Ogston's coccus, but potential, conditional, pathogens all the same. Clearly, we have a long way to go to understand their pathogenic mechanisms but perhaps comparative study of the various cocci in their various activities will yield helpful clues.

HOSPITALS BUILT FOR STAPHYLOCOCCI

Ogston's coccus can take credit for having had a substantial influence on the way we have built and worked surgical wards and operating departments over the past 40 years. The disappearance of the haemolytic

streptococcus as a prime cause of surgical wound infection, though not before case-to-case transfer of infection was recognized, and with it concentration of attention on staphylococci, occurred at a time when war-time experience on aerobiology was becoming available to study peace-time epidemics. And staphylococci are so easy to cultivate in the laboratory, and the phage-typing system was so readily adapted to the testing of large numbers of strains, that we have a great mass of information about the pattern of colonization and infection in surgical wards and maternity nurseries, as well as on the distribution of the infecting strains in the air, on blankets and on the floor. For no other microbe is there so much quantitative information.

Staphylococci are clearly transmissible between individuals, and some aspects of the transmission process have been discussed by Dr Lidwell. Very early in our own studies of spread in hospital wards we recognized what we thought were major differences in the extent to which different individuals managed to spread their cocci, and the temptation to think of abundant dispersers as 'dangerous carriers' was considerable. Again, previous experience with *streptococci* suggested that an important contribution to the control of spread of infection might flow from the recognition of dangerous dispersers. Ogston's coccus was however prepared to demonstrate its individuality. Both in studies at St Bartholomew's Hospital with Professor Shooter and in later studies at St Mary's Hospital, we found that most of the patients who were particularly apt to disseminate their commensal staphylococci into the air, actually carried staphylococci that seemed to have a rather poor potential for causing disease. Studies by Blowers and others have demonstrated the importance, for heavy dissemination, of carriage on perineal or trunk areas of skin; are there possibly preferential areas of skin colonized by less pathogenic strains of staphylococci?

Nevertheless it looked as though aerial dissemination must be a potent factor in the transmission of infection, and we have used this belief to encourage architects and planners to design hospitals to minimize the risk of air transfer—by elaborate ventilation systems (which rather too often fail to work) and by the provision and use of single rooms for isolation purposes. With the notable exception of the important work described by Dr Smylie, it has not been possible to demonstrate a clear effect on the transmission of staphylococci in hospital from subdivision of wards or the provision of single-bed isolation rooms as part of a ward complex. The recent work by Dr Lidwell in England and Dr Hambraeus in Sweden strongly suggests that part at least of the failure to control spread by controlling air-flow is attributable to the fact that the staphylococci are carried on clothing. Nevertheless, within the ward area the rate at which patients become nasal

carriers is clearly related to the numbers of staphylococci in the air of the ward, and Dr Lidwell's studies on this topic offer one of the very few real-life situations where it is possible to arrive at some sort of estimate of the average dose needed to establish colonization in man.

Elaboration of operating room design initially lay in further subdivision of the space and elaboration of the ventilation pattern. Recently the development has been towards restricting the area kept especially clean, by laminar flow ventilation or by the plastic isolators described by Mr McLauchlan. McLauchlan was unable to show any significant benefit, measured by the infection rate in patients having hip replacement, from the use of the Trexler isolator in the operating room, but did find benefit from a 'wound isolator' used to protect the wound in the post-operative period. These observations raise again the controversy on the relative importance of ward and operating room as the place in which surgical wounds become infected. Dr Smylie had previously also entered a strong plea on behalf of the ward.

CONCLUSION

Medical microbiologists owe a considerable debt of gratitude to Ogston's coccus. Apart from the employment it has provided—I estimate that the *Index Medicus* has cited well over 20 000 papers on pathogenic staphylococci during the past 30 years—it provided the first, or if not the first yet an excellent example, of a whole variety of phenomena. Many of these phenomena have been discussed in the present conference.

Staphylococci provided abundant opportunity for argument on nomenclature and, once we leave the realm of what Ogston described as Staphylococcus, for argument on taxonomy. The flowering of epidemiological and pathological studies in the late 1930s and 1940s owed much to the recognition of the taxonomic importance of coagulase; there is already evidence that the taxonomic clarifications being accepted for the 'other' staphylococci will likewise stimulate as well as facilitate epidemiological studies.

Staphylococci produce an enormous variety of extra-cellular products, many of which have been graced with the title of toxin; it is clear that microbiologists will continue to thrive on the variety of experiments that can be devised to explore the potential effect of these factors. One of them, incidentally, has opened up a whole new field of diagnostic technology; I refer to the so-called protein A which will link with the Fc fraction of immunoglobulin and is the basis of the fashionable co-agglutination tests and offers a method for the specific removal of IgG from a mixture.

Staphylococcal phage typing was, I think, second only to that for *S. typhi* and apart from persuading us to rely on recognition of complex patterns of reactions—which has had to be the method used for most subsequent systems —it also stimulated us into a proper analysis of reproducibility. An incidental advantage of the designation of types on the basis of complex patterns is that it curtails the microbiologists' well-known urge to collect types.

Application of the typing system enabled us to recognize different behaviour patterns among staphylococci having different phage susceptibilities, and we have been able to recognize, if not to explain, a series of changes in strains dominant in our hospital communities, which Professor Shooter has referred to as 'evolution'.

With typability, prevalence and clinical importance, Ogston's coccus has provided a superb marker for cross-infection in hospitals, and for tracing the spread of microbes by air. It is a chastening fact that, though the staphylococci seem to have evolved so that we no longer have those notorious 'epidemic types' of the 1950s and early 1960s, our patients still get staphylococcal wound infection. It is as if the cocci were laughing at us for thinking that it was as simple as it seems to have been with the haemolytic streptococcus.

Of course Ogston's coccus has been laughing at our attempts to circumvent the problem of keeping him out of wounds by the apparently simple plan of killing him when he gets there; the evolution of hospital staphylococci had demonstrated the remarkable versatility of the bacterial genome. The impressive acquisition of antibiotic resistance ensured that the staphylococci were early involved in the field of microbial genetics, although they had to wait until after some years of work with *E. coli* for recognition of the key importance of plasmid transfer by means of phage.

But as a background to all studies of the interaction between staphylococci and man, we have the intriguing question of what Ogston's coccus is doing for the propagation of its race when it quits the chaise-longue of the commensal carrier state for the hurly-burly of the active pyogenic infection. The carrier problem in infectious disease is now different from the one Ledingham wrote about in 1912 but still offers plenty of challenge both for scientific microbiology and preventive medicine.

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