Infection and colonization by the 'other' staphylococci

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> It is no doubt possible that there exist species of micrococci precisely similar to one another in appearance and growth, yet widely different in the effects they are capable of producing (Ogston, 1881).

It is evident that Ogston was aware of the difficulty of distinguishing the staphylococci that he had recognized as an important cause of wound sepsis from the rather similar organisms that lived harmlessly on the body surface. In the years that immediately followed his discovery, this problem appeared to have been solved. Workers who followed up his own observation that the colonies of staphylococci from purulent lesions—like the pus in these lesions—were often yellow in colour concluded that there was a single pathogenic species, orginally named *Staphylococcus pyogenes aureus* (Rosenbach, 1884) and now officially designated *S. aureus*. Colonial pigmentation was soon recognized to be an unreliable marker for this species, and the discovery of the coagulase reaction (Loeb, 1903–4) reinforced the view that the clump-forming gram-positive cocci comprised one species of pathogens, coagulase positive and usually forming yellow colonies, and a number of other species that were coagulase negative, variable in pigmentation, and harmless commensals.

This view survived the discovery, in the 1940s, that *S. aureus* also was a common skin commensal that only occasionally assumed a pathogenic role. As late as 1959, Elek reviewed the subject of staphylococcal disease without considering the possibility that any species other than *S. aureus* was pathogenic. The only question that appeared to be outstanding was whether the ability to clot plasma was the correct distinguishing character for the pathogenic species. The most widely held view was that, although this might not be the major determinant for pathogenicity, it was the best available marker for the production of a series of other extracellular substances that

acted in this way. This view has since been progressively eroded by observations in two fields.

(1) The coagulase-positive staphylococci form a much less homogeneous group than was once thought. Comparisons of strains isolated from man and other mammals show that very few of the supposed extracellular virulence factors are formed by the predominant strains from all animal species. We are thus left with a few toxins that play a part in the production of some of the disease manifestations in certain animal species, notably the α lysin, the epidermolytic toxins, the enterotoxins, and possibly the PV leucocidins, but few if any extracellular virulence factors that characterise the species as a whole. Thus, *S. aureus* came to be recognised as a loose grouping of host-adapted varieties or sub-species. Some of these, including the 'white' staphylococci of dogs and pigeons, have cell-wall and metabolic characters resembling those of the coagulase-negative species *S. epidermidis*. It is now proposed that they should be removed to a new species *S. intermedius* (L. R. Hill, this Symposium) in which they will join other strains, including 'S. hyicus'. which had previously been considered as *S. epidermidis*. At least some of the *S. intermedius* strains appear to cause disease.

(2) As long as the view was accepted that only coagulase-positive staphylococci were pathogenic, it seemed reasonable to ignore other staphylococci from superficial lesions. Even when isolated from the blood, there was a reluctance to accept their role as pathogens because of the possibility that they had been introduced accidentally in the course of collecting the sample. This view changed dramatically when, as a result of advances in surgical technique, serious and even fatal infections with coagulase-negative staphylococci appeared in sufficient numbers for the individual worker to study groups of cases both clinically and at necropsy. The opinion could still be held, however, that these were so-called 'opportunistic' infections and that the organisms were not 'real' pathogens. The subsequent recognition of a common but less severe infection by coagulase-negative staphylococci, acute urinary-tract infection in young women, itself a consequence of the introduction of quantitative urine-culture methods, finally disposed of the concept that 'pathogenicity' is confined to *S. aureus* and has led to a re-assessment of the meaning of this term in relation to staphylococci and micrococci (see Holt, 1971).

Conditional and Primary Pathogenicity

The invasion of tissues by bacteria that normally live a saprophytic existence is usually a consequence of increased susceptibility in the individual host. When this occurs, the organism can be considered to be

exhibiting *conditional pathogenicity,* as opposed to the *primary pathogenicity* of organisms that invade the tissues of healthy persons when presented to them by a natural route. Broadly, conditions that may determine invasion are: (1) injury to the body surface; (2) by-passing the surface defences by introducing the organisms artificially into deep tissues or into a normally sterile area such as the urinary or respiratory tract; (3) local depression of tissue resistance in an internal organ, so that small numbers of organisms transiently present in the bloodstream may settle down and multiply there; and (4) a deficiency in the general defence mechanisms, either innate or acquired. Conditional infections need not necessarily be severe, as is usually implied in current usage of the term 'opportunistic infection'; and the precipitating factors for them tend to be specific for the infecting organism.

Many *S. aureus* infections, including most of those acquired in hospital, are conditional in this sense, but there are other circumstances in which this organism acts as a primary pathogen. No-one who observed the outbreaks of furunculosis caused by the 80/81 strain among hospital nurses during the 1950s can doubt the ability of this strain to cause disease in the absence of predisposition.

When we examine the diseases caused by coagulase-negative staphylococci we shall see several examples in which the organisims act as conditional pathogens, and one clear instance of primary pathogenicity.

Diseases Caused by Coagulase-Negative Staphylococci and Micrococci

Systemic infections

Serious bacteriaemic infections attributed to coagulase-negative staphylococci, or to organisms loosely described as *'S. epidermidis',* occur only under certain clearly defined circumstances. Very much more rarely, similar infections may be caused by micrococci.

Endocarditis. During the earlier part of this century there were many isolated reports of the growth of coagulase-negative staphylococci from the blood under circumstances that suggested, with various degrees of certainty, that the organisms were responsible for the current illness (see Smith *et al.,* 1958). In a number of these cases, endocarditis was demonstrated, and there was often a history of previous damage to heart valves. From 1955 onwards, reports appeared of endocarditis due to coagulase-negative staphylococci developing after an open operation on the heart

(Denton *et al.,* 1957; Resnekov, 1959). Comparisons soon became possible between cases of post-cardiotomy and of spontaneously occurring endocarditis (Quinn, Cox & Fisher, 1965; Quinn, Cox & Drake, 1966; Geraci, Hanson & Giuliani, 1968). The former were usually cases of acute endocarditis due to penicillin-resistant strains and mortality-rates were high. The latter were of the subacute form and tended to affect patients with previous chronic heart damage; the staphylococci were often penicillin sensitive and the infection could usually be eradicated by treatment with antibiotics.

Post-cardiotomy endocarditis usually follows operations in which a rigid prosthesis is inserted and much less often the repair of septal defects or aorta-coronary bypass operations (Amoury, Bowman & Malm, 1966; Wilson, 1977; Blouse *et al.,* 1978). According to Arnett and Roberts (1977), the most consistent lesion in fatal prosthetic endocarditis is infection of tissues immediately adjacent to the site of attachment of the prosthesis to the valve ring, with abscess formation and frequent extension into nearby tissues; the appearance of vegetations is a less regular feature. Thus, prosthetic endocarditis is a true infection of cardiac tissue.

About one-half of all cases of post-cardiotomy endocarditis develop within 2 months of operation ('early' cases). Although the percentage distribution of various organisms as causes of 'early' and 'late' cases is somewhat different (table I), coagulase-negative staphylococci are responsible for about one-quarter in both groups. *S. aureus* causes rather less infections and these are more often early than late. Coagulase-negative staphylococci are responsible for nearly one-half of fatal infections and *S. aureus* for relatively few (Arnett & Roberts, 1977). In endocarditis of the natural heart valve, however, coagulase-negative staphylococci are among the uncommon causes (Cates & Christie, 1951; see also table I); and in endocarditis associated with the intravenous use of narcotic drugs they are very rare, even in patients with a previous history of valvular damage (Simberkoff, 1977).

In the days immediately after a cardiac operation, coagulase-negative staphylococci are sometimes isolated from the blood of patients who subsequently do not develop endocarditis. Their significance is difficult to assess, but coagulase-negative staphylococci—unlike gram-negative bacilli—appear rarely to cause febrile bacteriaemia without endocarditis after operations on the heart (Dismukes & Karchmer, 1977).

Infections associated with operations for the relief of hydrocephalus. A febrile illness, usually with splenomegaly and anaemia, may develop after the insertion of a valve to drain the cerebrospinal fluid into the atrium (Callaghan, Cohen and Stewart, 1961), or into the peritoneal cavity or a

ureter. The causative organism is usually present in the blood but less often in the cerebrospinal fluid (Schoenbaum, Gardner & Shillito, 1975). When drainage is into the atrium, coagulase-negative staphylococci are responsible for about one-half and *S. aureus* for about one-quarter of infections (Schoenbaum *et al.*, 1975). Over two-thirds of infections of ventriculo-atrial shunts occur within 2 months of the insertion of the device. Unlike post-cardiotomy endocarditis, the 'lesion' consists only of

TABLE I

Bacterial aetiology* of 'early'† and 'late' prosthetic-valve endocarditis, and of endocarditis of the natural heart-valve

Bacteria	Percentage frequency in		
	prosthetic endocarditis‡		endocarditis of natural valves§
	'early'	'late'	
Streptococci: not enterococci	7.3	26.6	47.5
Streptococci: enterococci	4.1	9.1	10.8
Staphylococcus aureus	20.0	14.3	21.6
Other staphylococci and micrococci	27.1	23.4	3.6
Diphtheroids	8.0	3.9	1.4
Gram-negative aerobes	19.8	12.2	7.9
Yeasts, moulds	11.9	5.9	0.7
None isolated	2.0	4.6	6.5

* Data from A. W. Karchmer & M. N. Swartz (1977), by permission of the authors and the American Heart Association, Inc.
† Within 60 days of operation.
‡ Total from 13 published series; 305 cases.
§ Massachusetts General Hospital, 1964–72; 139 cases.

a fibrinous vegetation on the prosthesis. The heart values are unaffected, even when the tip of the atrial catheter is in contact with the tricuspid valve. The infection is virtually impossible to eradicate by antibiotic treatment unless the prosthesis is first removed, when this is usually easily done.

Superficial infections

It is difficult to prove that coagulase-negative staphylococci cause infections of the skin or wounds, but no other organisms can be isolated from a number of wounds that show undoubted clinical signs of sepsis. According to Wilson & Stuart (1965), this was true of 4.4 per cent of apparently septic wounds. As we shall see, careful studies of wound infections after operations on the heart suggest that here the proportion may be considerably greater, and in a few of the cases osteomyelitis of the sternum develop subsequently. Wound sepsis associated with coagulase-negative staphylococci often precedes the appearance of post-cardiotomy endocarditis.

Feigin *et al.* (1973) believe that coagulase-negative staphylococci are occasional causes of acute otitis media on the evidence that they can be isolated in pure culture from pus aspirated through the intact ear-drum. Their ability to cause neonatal conjunctivitis is more doubtful. They are nearly always present in acne lesions, but it is unlikely that they initiate these.

The suggestion has been made (Varadi and Saqueton, 1968) that strains of coagulase-negative staphylococci with strong elastolytic activity—a character said to occur in some 30 per cent of *S. epidermidis* strains—are responsible for perifollicular macular atrophy, in which circular flattened areas appear around hair follicles. It has also been suggested that elastase-forming coagulase-negative staphylococci may play some part in periodontal disease (Murphy, 1974; see also Hartman & Murphy, 1977).

Deep infections in wounds

Infections around joint prostheses may yield only coagulase-negative staphylococci; these may develop months or years after the insertion of the prosthesis, but other similar lesions yield sterile pus. Whether the organisms are the cause of the inflammation is difficult to determine.

Urinary-tract infection

It had long been suspected that coagulase-negative staphylococci caused mild urinary-tract infection in hospital patients after operations on or catheterisation of the tract. Then, in 1962, Pereira claimed that urinary-tract infections in women were caused by coagulase-negative staphylococci with two characteristic properties: possession of a unique surface antigen and resistance to novobiocin. Mitchell (1964, 1968) then defined two distinct patterns of urinary-tract infection: (1) in hospital patients of either sex, after some form of instrumentation, infections caused mainly by

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members of Baird-Parker's (1963) subgroup SII, now known as *S. epidermidis* biotype 1 (Baird-Parker, 1974), which are usually novobiocin sensitive, and (2) in healthy women outside hospital, infections caused by a novobiocin-resistant organism, first described as M3 but now designated *S. saprophyticus* biotype 3 (Baird-Parker, 1974).

The clinical pattern of infections caused by the *S. saprophyticus* strain has since been more precisely defined (Mabeck, 1969; Kerr, 1973; Maskell, 1974; Meers, White and Sandys, 1975; Sellin *et al.*, 1975; Pead, Crump and Maskell, 1977; Gillespie *et al.*, 1978). Sufferers are nearly all previously healthy females aged 16–25 years, with a few aged 26–45 years. An attack often occurs soon after a woman begins to be sexually active, but sexual promiscuity does not appear to be a determining factor. The local symptoms resemble those of urinary-tract infection caused by *Escherichia coli,* but severe general symptoms are less common; however, many of the patients give evidence of pyelitis. The disease appears to clear up spontaneously.

Identity and Sources of the Pathogenic Strains

The conditional pathogens

Nearly all of the organisms responsible for systemic infections and for hospital-acquired urinary-tract infections, and those isolated from surgical wounds, are classifiable as *S. epidermidis* as defined by Baird-Parker (1974). When examined in greater detail, most of them belong to his biotype 1. This was clearly established for urinary strains by Mitchell (1968), for strains from cerebrospinal-shunt infections by Holt (1969), and strains from a variety of clinical specimens by Mitchell, Alder & Rosendal (1974) and Males, Rogers & Parisi (1975). However, most of these and similar series include a small number of other strains allocated to *S. epidermidis* biotypes 3 and 4 or even to *S. saprophyticus* biotypes (Baird-Parker, 1974). True micrococci are very rarely seen. Table II shows the distribution among Baird-Parker (1974) biotypes of strains isolated from the blood and internal organs of a carefully selected series of patients believed on good evidence to have been suffering from a systemic infection (Marples & Richardson, 1981).

When classified according to the alternative scheme of Kloos and Schleifer (see L. R. Hill, this Symposium), at least nine species of staphylococci can be recognized in the human body flora (Kloos & Musselwhite, 1975). These species show some correspondence with the Baird-Parker (1974) biotypes of

TABLE II

Classification of 141 independent isolates of coagulase-negative staphylococci or micrococci from systemic infections* according to Baird-Parker (1963), and present designations according to Baird-Parker (1974)

Designation according to Baird-Parker (1974)	Designation according to Baird-Parker (1963)	Number of cultures
S. epidermidis		
biotype 1	SII	111
	SV	6
biotype 2	SIII	0
biotype 3	SIV	10
biotype 4	SVI	6
	S sp.	2
S. saprophyticus		
biotype 1	M1	1
biotype 2	M2	0
biotype 3	M3	4
biotype 4	M4	0
Micrococcus sp.	M6	1

* Collected by participants in the International Collaborative Study on the Phage-typing of Coagulase-negative Staphylococci from nine centres in eight countries; examined by Dr R. R. Marples.

TABLE III

Classification of 141 independent isolates of coagulase-negative staphylococci or micrococci* from systemic infections in the Kloos-Schleifer scheme (Kloos *et al.*, 1974; Kloos & Schleifer, 1975)

Designation	Number of cultures
S. epidermidis	111
S. warneri	4
S. hominis	11
S. haemolyticus	2
S. capitis	8
S. xylosus	1
S. cohnii	4

*See table II; examined by Dr R. R. Marples.

S. epidermidis and *S. saprophyticus,* but this is far from complete (Marples, 1980; L. R. Hill, this Symposium). Information about the distribution of isolates from systemic infections (see table II) among the Kloos-Schleifer species is given in table III. It will be seen that the numbers of strains allocated to *S. epidermidis* (Kloos & Schleifer, 1975) and to *S. epidermidis* biotype 1 (Baird-Parker, 1974) were identical; strain-by-strain correspondence approached 100 per cent.

According to Kloos & Musselwhite (1975), *S. epidermidis,* as defined by them, comprises the majority of the staphylococcal population of the skin of the anterior nares, the head, and the axilla in adults. Several other species predominate on other skin areas in varying proportions of subjects, but their distribution is irregular and varies with time and geographical location. Comparison of this distribution pattern with the frequency of isolation of the other staphylococcal species from systemic infections is thus difficult.

The true micrococci (Baird-Parker, 1974) form a considerably greater proportion of the flora of the skin—except of the nose and axilla—than of strains isolated from systemic infections. They form a constant minority population of 1–20 per cent of all aerobic organisms on the head, legs and arms in 80 per cent of persons. Although the micrococci as a whole are rarely implicated in systemic infections (tables II and III) one micrococcal strain appears to be particularly associated with post-cardiotomy endocarditis; Marples & Richardson (1980) have collected strains isolated from six such patients. It has very uniform characters, including methicillin resistance, but it does not conform to the description of any named micrococcal species (Baird-Parker, 1974; Kloos, Tornabene & Schleifer, 1974).

Can the frequency of *S. epidermidis* biotype 1 in systemic lesions be attributed entirely to its predominance in the flora of the skin of the upper part of the body, or is it, or are some strains of it, more 'virulent' than other coagulase-negative staphylococci?

It has been stated that *S. epidermidis* biotype-1 strains are more active producers of extracellular enzymes than are members of other biotypes (Males, Rogers & Parisi, 1975), and that *S. epidermidis* strains from lesions are more active in this respect than strains from carrier-sites (Heczko, Kasprowicz & Kucharczyk, 1971). The products said to be formed include α, β and δ lysins, succinic-oxidase factor, and various lipases and proteases (Heczko *et al.,* 1971; Marsik & Parisi, 1973; Gemmell & Roberts, 1974; Males *et al.,* 1975). It has even been suggested that the *S. epidermidis* strains responsible for infections are intermediate in character between *S. aureus* and the carrier strains of *S. epidermidis.* These conclusions cannot yet be accepted without question; they await confirmation by the examination of

more carefully selected collections of supposedly pathogenic strains, and by a more detailed characterization of the haemolytic toxins claimed to be common to *S. aureus* and *S. epidermidis*.

According to Murphy (1974) elastase-forming strains of *S. epidermidis* produce more of this enzyme than do *S. aureus* strains. A polysaccharide capsule with antiphagocytic properties has been described in *S. epidermidis* (Yoshida, Ichiman & Ohtomo, 1976) but has not yet been related to the ability to cause serious disease.

Primary infection in the urinary tract

The organisms responsible for urinary tract infection in young women have reasonable uniformity of characters when examined by the tests used by clinical microbiologists: the Baird-Parker biochemical tests and antibiotic-resistance pattern. This suggested that the primary urinary pathogen was a single entity, but difficulties were encountered when attempts were made to identify similar organisms in the normal body flora. Thus, it became apparent that novobiocin resistance was not entirely confined to *S. saprophyticus* biotype 3, that members of this biotype isolated from the skin were often novobiocin sensitive, and that both urinary and skin isolates fell into several species in the Kloos–Schleifer system (Nord *et al.*, 1976; Hovelius & Mårdh, 1977; Namavar, de Graaff & MacLaren, 1978b). In general (Namavar *et al.*, 1978b), *S. saprophyticus* biotype-3 strains (Baird-Parker, 1974) from the urine are nearly all resistant to novobiocin; most of them belong to the Kloos–Schleifer species *S. saprophyticus* but a few of them are *S. cohnii* or *S. warneri*. However, members of this Baird-Parker biotype from the skin include some 40 per cent that belong to the predominantly novobiocin-sensitive Kloos–Schleifer species *S. haemolyticus* and *S. capitis*; the rest are members of the three mainly novobiocin-resistant species found in the urine, but *S. cohnii* predominates. Kloos & Musselwhite (1975) found that *S. saprophyticus* (Kloos–Schleifer) which corresponds to the majority of the urinary strains, forms a small proportion (1–20 per cent) of the staphylococci on the arms and legs of about one-half of the population, but is rarely present in the nares or the axilla. No other carriage site at which it predominates has yet been found. It is rarely present in the urethra of normal women or the urethra or prepuce of males (Sellin *et al.*, 1975; Mårdh & Hovelius, 1977). According to Pead & Maskell (1977), it can be isolated from the rectal swabs of 7 per cent of women, but Gillespie *et al.* (1978) could not confirm this.

The characters of the urinary pathogen so far observed in the laboratory provide a few clues to the means by which it invades the bladder. Its ability

to multiply in urine is no greater, and may indeed be less, than that of other coagulase-negative staphylococci (Anderson *et al.*, 1976). Extracellular substances of possible significance have not been identified. Most strains, whether classified as *S. saprophyticus* or *S. cohnii,* have a common cell-wall teichoic acid (Aβ C; Oeding & Digranes, 1977), but no role has yet been ascribed to this. Although coagulase-negative staphylococci are non-pathogenic for the adult mouse, Namavar *et al.* (1978a) observed that novobiocin-resistant *S. saprophyticus* biotype-3 strains (Baird-Parker, 1974) from the urinary tract were consistently more virulent for infant mice by the intracerebral route than was *S. epidermidis* biotype 1 or *S. saprophyticus* biotype 1 or 2. The same was true of novobiocin-resistant but not of novobiocin-sensitive biotype-3 strains from the skin. However, when the strains were re-classified in Kloos–Schleifer scheme, intracerebral virulence appeared to be a feature of novobiocin-resistant strains of both species *S. saprophyticus* and *S. cohnii* whether isolated from the urine or the skin. Thus, virulence for the infant mouse does not exactly parallel the ability to invade the urinary tract.

Hovelius & Mårdh (1979) studied the agglutination of sheep erythrocytes by members of various staphylococcal species (named in the Kloos–Schleifer system); nearly all strains of *S. saprophyticus* possessed a trypsin-sensitive, D-mannose-resistant haemagglutinin which was rarely found in *S. aureus, S. epidermidis* or *S. cohnii.* According to Mårdh *et al.* (1979), *S. saprophyticus* has a specific ability to adhere to exfoliated epithelial cells from the urinary tract but not to other epithelial cells. Whether, as suggested by Hovelius *et al.* (1979), it is also responsible for some cases of non-gonococcal urethritis in males is uncertain.

Present evidence suggests that the urinary-tract infection of young women is by the ascending route, and that the causative organism forms only a minority of the skin staphylococci that reach the bladder as a result of physiological processes.

Routes of Infection with Coagulase-Negative Staphylococci in Hospital

Over one-half of the systemic *S. epidermidis* infections associated with cardiotomy occur within 1 month of operation (Arnett & Roberts, 1977; Blouse *et al.,* 1978). In a large series of cerebrospinal-shunt operations (Schoenbaum *et al.,* 1975), 61 of 98 infections appeared in the 1st month, and in months 2–3 and 4–11 the average infection-rates were respectively 4.5 and 1.5 per month. There is thus reason to believe that the infecting

organism is usually introduced at or around the time of operation. Whether late infections often result from an initial infection is not known, but Marples *et al.* (1978) describe one patient in whom a particular strain was isolated from a cardiotomy wound soon after operation and in whom the same strain caused endocarditis 6 months later. On the other hand, Williams *et al.* (1979) believe that late-onset prosthetic endocarditis may be precipitated by a mild skin infection or the giving of intramuscular injections.

In the hospital, the infecting strain may have come from the patient's own flora or from that of a member of the hospital staff or another patient. Information about this, or about the route of transmission of the organism, is very scanty. This is partly because of the difficulty of identifying individual strains of *S. epidermidis* in the laboratory. Biochemical characters and antibiotic-resistance patterns are somewhat unstable (Bentley *et al.*, 1968; Marples *et al.*, 1978), and small differences between strains have often to be ignored. Many different phage-typing systems are in use (see Pulverer, Heczko & Peters, 1979). They differ considerably in reported typability rates and in their ability to distinguish between strains. Reproducibility of results under field conditions is at present under investigation in an International Collaborative Study, but early results are not encouraging (de Saxe *et al.*, 1981).

Most hospital-acquired infections are sporadic, and the number seen in any one hospital is usually quite small. Thus, prospective studies of all possible sources of infection—with multiple-site swabbing of patients and staff—are exceedingly onerous, and few have been reported. Many studies of the distribution of *S. epidermidis* in the environment of the operating room have been made. Considerable significance was attached to the isolation of this organism from the blood in the extracorporeal circulation, but it is difficult to relate these observations, which were seldom quantitative, with the risk of infection. The strains responsible for infections in cardiac-surgery departments are almost invariably resistant to several antibiotics, as are many of the strains isolated from staff members and other patients. However, resistance patterns alone are seldom specific or stable enough to be of value in epidemiological investigations.

Epidemics of infection associated with cardiac operations

Episodes of increased incidence of *S. epidermidis* infection in cardiothoracic departments have been described, but do not appear to be common. They provide good opportunities for the intensive investigation of the circumstances in which infection occurs.

Hammond & Stiver (1978) recorded nine cases of *S. epidermidis* endocarditis after 308 valve-replacement operations performed by one surgical team in 8 months. Only three of the infections were 'early', but the circumstances suggested that the infections had occurred at or near the time of operation. In the previous 3 years there had been no such infections after 213 similar operations.

Blouse *et al.* (1978) described an incident in which seven cases of bacteriaemic illness (with four deaths) and 18 wound infections, attributed to *S. epidermidis,* occurred in the space of 1½ years. The median time from operation to onset was 6 days. The phage-typing results suggested that two strains had been responsible, one in the earlier and the other in the later part of the outbreak. The first strain was prevalent in nasal swabs of the staff of the unit early in the incident; it was later replaced by the strain responsible for the later cases. Extensive environmental sampling towards the end of the outbreak revealed *S. epidermidis* in the cardio-pulmonary bypass pump on 13 per cent of occasions, and strains prevalent in the nose of staff members were isolated on several occasions (Lathrop, Brockett & Blouse, 1978). A few isolations were also made from valve prostheses immediately before insertion. It was concluded that the operating team was the main source of infection, which had probably reached the patients by the aerial or contact route, or via the bypass pump. A package of preventive measures, including the installation of a laminar-flow enclosure, strengthening surgical discipline and the reduction of the case-load, was introduced; only one *S. epidermidis* infection was seen in the following 15 months.

A third outbreak (Marples *et al.,* 1978) occurred in a surgical unit in which a prospective study of infection associated with cardiotomy was in progress. Very many isolates of *S. epidermidis* from patients and staff were stored and examined subsequently. During 14 months, bacteriaemic illnesses developed in 15 patients after the insertion of a prosthetic valve, of which 12 were caused by *S. epidermidis* biotype 1. In all, 57 patients showed clinical evidence of wound sepsis after 382 operations, and from 24 of these *S. epidermidis* (some four-fifths of biotype 1) was the only organism isolated. Six of the 12 bacteriaemic infections with *S. epidermidis* biotype 1 followed wound sepsis associated with this organism. Detailed study of all the cultures suggested that a number of them belonged to a single strain (A); though not identical in every respect, they showed a general conformity in biochemical characters, antibiograms and conventional phage-typing patterns; their identity was finally confirmed by 'reverse' or lysogenicity typing (de Saxe & Notley, 1978). Retrospective analysis of the data showed that this 'strain A' had caused clinical infections in 8 patients in 9 months; 7 of the patients were considered to have had endocarditis and 5 of them died;

one had a wound infection only. Nearly all of the isolates from serious infections, and all of 'strain A', were resistant to 4–6 antibiotics.

Nose and hand swabs had been collected from the patients pre-operatively, and finger-tip cultures were made from the staff at intervals during the study. These revealed a situation quite different from that described by Blouse *et al.* (1978). *S. epidermidis* strains from the patients before operation, from the senior surgical staff and the operating-theatre nurses were predominantly sensitive to antibiotics other than penicillin, though a considerable minority of the junior surgical staff yielding strains resistant to four or more antibiotics. However, 'strain A' was isolated from only one staff member—a surgeon—on one of the six sampling occasions, and it was never isolated from a patient preoperatively. Unfortunately, sampling of the staff of the postoperative ward, and of uninfected patients postoperatively, was not undertaken during the period of the 'strain A' outbreak. When this was done later, it was found that the predominant strains in both groups were resistant to 4–6 antibiotics. These findings suggested that infection was unlikely to have been introduced in the course of the operations and that the main source of infection was probably in the postoperative ward.

SUMMARY

Staphylococcus epidermidis is a conditional pathogen: it causes disease in man only in the presence of certain clearly defined predisposing conditions. It is (1) a major cause of endocarditis after the insertion of a heart-valve prosthesis, and an uncommon cause of endocarditis of the damaged natural heart-valve; (2) the predominant cause of chronic bacteriaemia after the insertion of cerebrospinal-fluid shunt-device; and (3) responsible for a small proportion of the urinary-tract infections that occur after catheterization of or operation on the bladder. Its ability of cause wound sepsis is limited, but its presence in an inflamed wound often precedes the development of a systemic infection.

Apparently identical organisms form a majority of the staphylococcal flora of the skin of the upper part of the body. Whether all of them are of similar pathogenicity is uncertain, but the fact that certain identifiable strains are responsible—though infrequently—for epidemics of infection in cardiac-surgery departments suggests that this may not be so. No markers for potential pathogenicity have yet been identified.

The strains responsible for post-cardiotomy infections are resistant to several antibiotics, as are many of those carried by other persons in the

same hospital department. The infection appears usually to have been transmitted at or soon after the time of operation, but systemic manifestations may develop many months later. The scanty evidence available suggests that transmission may occur not only in the operating room but in the post-operative ward.

A quite different coagulase-negative staphylococcus—a novobiocin-resistant member of biotype 3 of *S. saprophyticus* (Baird-Parker, 1974)—is a primary pathogen responsible only for urinary-tract infection. It causes this in previously healthy young women outside hospital, and appears to reach the bladder by the ascending route. Staphylococci with the ability to infect under these circumstances appear to form a rather small proportion of those present at any carriage site. Several laboratory markers for this type of pathogenicity have been described; of these, only the ability to adhere to epithelial cells of the urinary tract appears to be of possible significance for pathogenesis.

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