# STAPHYLOCOCCAL SEPTICAEMIA AND PYAEMIA

## A REVIEW OF CASES AT GROOTE SCHUUR HOSPITAL OVER THE PAST NINE YEARS

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The vast and growing literature concerning staphylococcal infections is testimony to the great importance of this organism in all branches of medicine and surgery. Because of its ubiquitous nature and the ease with which it develops resistance to antimicrobial drugs, it has now reached a position of pre-eminence in the problem of bacterial infections, especially those acquired within hospitals.[1-4]

Of the various forms that staphylococcal infections may take, none is of greater interest than those in which the organism enters, and can be cultured from, the blood stream. This may be a septicaemia, a pyaemia or a simple bacteraemia. The term staphylococcaemia is used in this article specifically to describe any condition in which staphylococci can be cultured from the blood stream in association either with a clinical picture of septicaemia or with pyaemic lesions caused by the same organism. These patients are found in all departments of a general hospital and provide the clinician with what can be one of the most difficult and intriguing problems in diagnosis and treatment. A review was undertaken of all such patients over the age of 11 years admitted to Groote Schuur Hospital during the nine-year period 1953 - 1961 inclusive.

### METHODS AND MATERIAL

#### *Methods*

The records of the Bacteriology Department were used to compile a complete list of blood cultures positive for staphylococci during the period reviewed. When the organism was identified as a coagulase-negative *Staph. albus*, it was assumed to be a contaminant unless grown from more than one bottle or on more than one occasion. Where these organisms were considered pathogenic, and in all instances where a coagulase-positive *Staph. aureus* was cultured, the patient's clinical notes (if available) were examined. If the clinical notes and other special investigations fitted a diagnosis of staphylococcaemia, the case was included in the series. In addition, autopsy reports for the period under review were checked for cases proved at autopsy, but where positive blood cultures had not been obtained during life.

#### *Total Numbers*

During these 9 years blood cultures positive for *Staph. aureus* were obtained from 412 patients. In only one patient, to be discussed later, was a culture of *Staph. albus* thought to be indicative of disease. Of these cultures, 154 were from children below 12 years of age and were not considered further, and in 25 cases the clinical notes could not be traced. Each of the remaining 234 cases was carefully considered to decide whether the blood culture indicated staphylococcaemia or represented a contaminant or non-significant bacteraemia. The minimum criterion accepted was a positive blood culture from a patient with the clinical picture of septicaemia or pyaemia (including acute osteitis and acute septic arthritis). Doubtful cases and cases where the information was inadequate were rejected. In this way 111 cases were accepted (110 patients, 1 with 2 attacks) and 123 cases rejected.

Because of the frequency with which staphylococci grown in blood cultures are not clinically significant, the interpretation of positive cultures can be a very difficult problem. In order to test whether the number of culture bottles in which growth occurs is a useful guide to the clinician, the above selection was made without regard to this point and the results were then analysed. Of 224 cases in which more than one blood-culture bottle was submitted on the first occasion, growth was reported

TABLE I. NUMBER OF BLOOD-CULTURE BOTTLES IN WHICH GROWTH OCCURRED ON THE FIRST OCCASION WHEN MORE THAN ONE BOTTLE WAS SUBMITTED

| | *Total* | *Staphylococcaemia* | *Non-significant* |
|---|---|---|---|
| Growth in all bottles .. .. .. | 113 | 90 (80%) | 23 (20%) |
| Growth in less than all bottles .. | 111 | 17 (15%) | 23 (20%) |

in all bottles in 113. The analysis in Table I indicates the significance of this information.

A search of the autopsy records brought to light only 3 cases of staphylococcal pyaemia in which positive blood cultures had not been obtained during life. This brings the total number of cases in the series to 114. There were 45 deaths, giving a mortality rate of 40%. If the cases of acute osteitis are excluded, the mortality figure becomes 57%. Autopsies were carried out in 23 of the fatal cases. The racial incidence was as follows:

| | *Total* | *Deaths* | *Mortality rate* |
|---|---|---|---|
| White | 43 (37) | 21 (20) | 49% (54%) |
| Non-white | 71 (40) | 24 (24) | 34% (60%) |

The figures in parenthesis exclude cases of acute osteitis and are more useful for comparison with other series.

The annual incidence was:

| *Year* | *Number* | *Deaths* | *Mortality rate* % |
|---|---|---|---|
| 1953 .... .... .... .... | 9 | 5 | 56 |
| 1954 .... .... .... .... | 11 | 3 | 27 |
| 1955 .... .... .... .... | 11 | 5 | 45 |
| 1956 .... .... .... .... | 13 | 5 | 38 |
| 1957 .... .... .... .... | 13 | 4 | 31 |
| 1958 .... .... .... .... | 17 | 6 | 35 |
| 1959 .... .... .... .... | 9 | 4 | 44 |
| 1960 .... .... .... .... | 20 | 8 | 40 |
| 1961 .... .... .... .... | 11 | 5 | 45 |

This shows that there has been no great change in incidence and mortality during the 9 years.

#### *The Overall Picture*

Of the 114 cases the majority fell into a few clear-cut groups:

*Present address: Hammersmith Hospital, London.

| | No. | % |
|---|---|---|
| Acute osteitis | 37 | 32 |
| Acute septic arthritis | 3 | 3 |
| Septic abortions | 19 | 17 |
| Postpartum sepsis | 1 | 1 |
| Postoperative cases and cases with septic intravenous drip sites | 17 | 15 |
| Major traumatic cases | 4 | 4 |
| Breast abscess | 1 | 1 |
| Total | 82 | 73 |

The remaining 32 cases were associated with a wide variety of general medical conditions. Usually the associated conditions were multiple, but in 5 cases the disease appeared to be spontaneous in previously healthy persons.

*General Aetiological Factors*

Among the whole group the incidence of certain aetiologically important factors was as follows:

| | | |
|---|---|---|
| Skin lesions as a possible source of staphylococcaemia | | 19 |
| Boils | 5 | |
| Pustules | 6 | |
| Infected cuts | 4 | |
| Bed sores | 1 | |
| Pemphigus | 1 | |
| Stevens-Johnson syndrome | 1 | |
| Exfoliative dermatitis | 1 | |
| Diabetes (4 in severe ketosis) | | 9 |
| Treatment with steroid drugs | | 8 |
| Renal failure | | 9 |
| Acute renal failure | 2 | |
| Chronic pyelonephritis | 7 | |
| Pre-existing rheumatic heart disease (becoming the site of staphylococcal endocarditis) | | 4 |
| Carcinomatosis | | 2 |
| Acute leukaemia | | 3 |
| Advanced liver failure | | 2 |
| Acute-on-chronic pancreatitis | | 1 |

CLINICAL AND PATHOLOGICAL FEATURES OF THE WHOLE SERIES

*Temperature, leucocyte count and sedimentation rate.* Figs. 1, 2 and 3 show, respectively, the temperature, leucocyte count and sedimentation rate of those patients in the series for whom this information was available. The figures are those recorded on admission or when staphylococcaemia first presented as a clinical problem. Those patients in whom the figures were likely to have been distorted by an underlying condition (e.g. leucocyte count in cases of leukaemia) were excluded. The degree of pyrexia on admission was consistently high. Of 70 patients, none had a temperature of less than 100°F. and the largest group lay between 103·0° and 103·9°F. The leucocyte count was under 10,000 per c.mm. in 14 out of 73 patients and the mean figure for the group was about 17,500 per c.mm. The sedimentation rate showed a wide scatter, but was below 20 mm. in the 1st hour in only 3 out of 59 patients.

*Secondary skin lesions* were recorded in 25 patients as follows:

| | |
|---|---|
| Purpura | 10 |
| Vesicles and pustules | 7 |
| 'Splinter' haemorrhages | 4 |
| Urticaria | 4 |
| Erythematous eruptions | 3 |
| Tender digital nodules | 3 |
| Herpes zoster | 1 |

On 3 occasions the causative *Staph. aureus* organism was isolated from a secondary skin lesion.

*Splenomegaly* was recorded in the notes of 12 patients, in 5 of whom an underlying medical condition was likely to have been the cause of the enlargement. An additional 2 cases showed abscesses of the spleen at autopsy.

*Retinal lesions* were recorded in only 4 patients, a surprisingly low figure, even if one assumes that they might have been missed in an equal number of cases.

*Jaundice* was seen in 12 patients, in only 3 of whom was there known to be underlying liver disease.

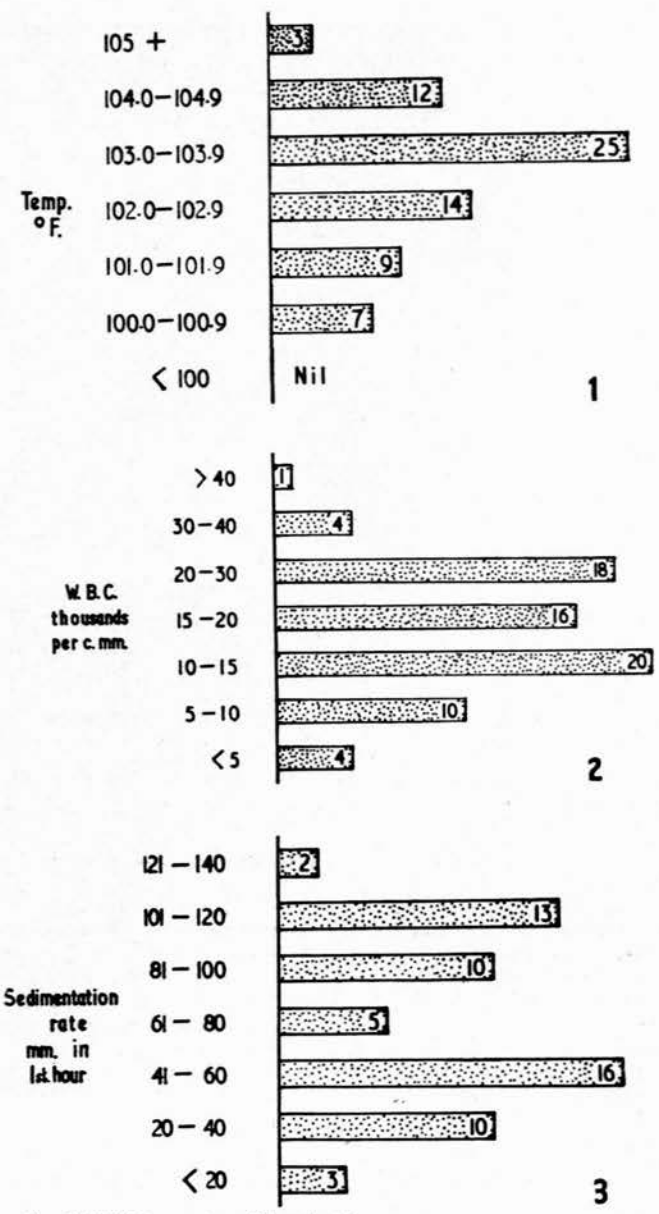


*Fig. 1.* Initial temperature (70 patients).
*Fig. 2.* Initial leucocyte count (73 patients).
*Fig. 3.* Initial erythrocyte sedimentation rate (59 patients).

*Thrombophlebitis* occurred in 7 patients, excluding those in whom it developed secondarily to septic intravenous sites (discussed below). There was one case of *cavernous sinus thrombosis.*

*Anaemia* appeared to be an almost constant accompaniment of staphylococcaemia, and most prolonged cases required repeated blood transfusions.

*Acute septic arthritis* was the presenting feature in 3 cases and developed during the course of a further 22.

*Diarrhoea* was mentioned in the notes of 6 patients and in 3 of them staphylococci were cultured from the stool.

*Soft-tissue abscesses* in muscles or subcutaneous tissues occurred in 13 patients.

*Mycotic aneurysms* were found at autopsy in 2 cases (both also had endocarditis). In one the aneurysm was in a sinus of Valsalva; the other case had aneurysms of the popliteal and

carotid arteries, the liver and the mesentery of the small intestine. The mesenteric aneurysm had ruptured and produced a fatal intraperitoneal haemorrhage.

*Cardiac Complications*

*Endocarditis* was diagnosed in 18 patients, 11 of whom died, giving a mortality rate of 61%. Autopsies were performed on all the fatal cases. In 3 it is uncertain which valves were affected. In the remaining cases the heart valves were affected as follows: Mitral 10, aortic 4, pulmonary 1, and tricuspid 1.

The important association between endocarditis and cerebral complications was confirmed by finding that 9 of these 18 cases (50%) had evidence of serious intracranial embolic lesions.

In 4 patients the staphylococcal endocarditis affected mitral valves previously damaged by rheumatic endocarditis. In two of these the endocarditis occurred without any other predisposing cause, in the third it followed a septic incomplete abortion and the fourth case followed open-heart surgery. This last case is of particular interest for a number of reasons:

*Case history No. 104.* A white male of 38 years was known to have had rheumatic heart disease and, following subacute bacterial endocarditis in 1954, was left with severe mitral incompetence. In November 1960 mitral valvuloplasty, with insertion of a baffel, was performed. Signs of mitral incompetence recurred, however, and the operation was repeated in February 1961. During the immediate postoperative period steroids were given. On the ninth postoperative day he developed a pyrexia, and blood cultures on 2 successive days grew the identical coagulase-negative *Staph. albus* from both bottles. On antibiotic therapy he made an uninterrupted recovery. Soon after discharge he had some teeth extracted (without antibiotic cover) and soon began to experience fever and malaise. When readmitted he had signs of mitral incompetence and a coagulase-positive *Staph. aureus* (with a different sensitivity pattern) was cultured from his blood on 4 occasions. He again responded to antibiotics, but on the seventh day developed a right-sided hemiplegia and aphasia. These improved, but he was left with a pseudobulbar palsy.

*Comment.* The bacteriological information in this case has been checked and there seems to be no doubt that the patient had 2 separate attacks of staphylococcal endocarditis, the organism in the first attack being a definite coagulase-negative *Staph. albus.*

*Pericarditis* occurred in 16 cases. In 14 of these the diagnosis was made clinically on the basis of a pericardial friction rub with or without electrocardiographic (ECG) or X-ray changes. In two further cases an effusion was aspirated, one of these being a massive effusion of almost pure blood.

*Myocarditis.* One 13-year-old child with acute osteitis developed cardiac failure with striking ECG changes and was diagnosed as having 'myocarditis'. For the rest, myocardial lesions were limited to pyaemic abscesses found at autopsy. There were 7 such cases; in 2 the abscesses were large and single, in the remaining 5 they were small and multiple. It is of interest that 5 of the cases with myocardial abscesses had endocarditis of the valves of the left side of the heart.

*Pulmonary Complications*

Pulmonary or pleural complications were noted in 47 cases. The frequency with which the various conditions were diagnosed by clinician, radiologist or pathologist was as follows:

| | |
|---|---|
| Pneumonia | 27 |
| Pulmonary infarction | 7 |
| Multiple lung abscesses | 7 |
| Multiple thin-walled cysts | 1 |
| Pleural effusion | 9 |
| Frank empyema | 1 |
| Pneumothorax | 3 |

In no instance did an obvious staphylococcal pneumonia precede the generalized staphylococcaemia, but it is obviously difficult to judge this in many cases. The occurrence of pneumothorax is of interest. Hay[5] suggested that it is due to septic infarction.

*Renal Complications*

Renal complications were present in a total of 42 cases. On the available information they were classified as follows.

| *Condition* | *No.* |
|---|---|
| 1. Chronic pyelonephritis antedating the staphylococcaemia | 7 |
| In 4 of these cases *Staph. aureus* was isolated from the urine, and in the 6 patients in whom it was tested the blood-urea level was over 100 mg. per 100 ml. One of these was a diabetic with necrotizing papillitis | |
| 2. Staphylococcaemia developing during the course of acute renal failure | 2 |
| Both these patients developed staphylococcaemia during the diuretic phase of acute tubular necrosis. One was a postoperative case (embolectomy) with mitral stenosis, boils and wound sepsis; the other followed a septic abortion | |
| 3. Fatal cases of staphylococcaemia in which autopsy revealed renal abscesses or infarcts | 14 |
| 4. A fatal postoperative staphylococcaemia in which an incidental autopsy finding was polycystic kidneys, a few of the cysts being infected with *Staph. aureus* | 1 |
| 5. Other patients in whom pyuria, marked proteinuria, haematuria or elevated blood-urea levels were recorded, but for whom there was insufficient information to make an exact pathological diagnosis. (Powell[6] suggested that staphylococcaemia may produce a variety of important non-suppurative renal lesions) | 17 |
| 6. A patient in whom acute renal failure developed during the course of staphylococcaemia | 1 |

This last patient was of considerable interest, and the exact cause of the renal failure remains uncertain:

*Case history No. 89.* A 35-year-old white male was admitted with fever, severe lumbar pain and oedema of the back. There was mild sepsis in a small fish bite sustained 2 weeks before. No cause was found for the pain and oedema of the back, but blood cultures positive for *Staph. aureus* were obtained. Some days after admission he went into acute oliguric renal failure, requiring dialysis on the artificial kidney twice. He finally recovered after a protracted course during which he developed pyaemic staphylococcal lesions in a number of sites. Residual renal function was good.

*Comment:* Partly because of extreme and rapid fluctuations in the urinary output during the acute stage it was felt that his renal failure might have been due to some type of obstructive ureteritis rather than acute tubular necrosis.

*Central Nervous System Complications*

Pyaemic lesions of the central nervous system are the most dangerous complications of staphylococcaemia. The following lesions were encountered (autopsy diagnosis where available, otherwise clinical):

| | Number | Deaths |
|---|---|---|
| Subarachnoid haemorrhage (hemiplegia 3, fits 1) | 5 | 5 |
| Hemiplegia | 5 | 3 |
| Two parietal abscesses (hemiplegia) | 1 | 1 |
| Fronto-parietal intracerebral haemorrhage (hemiplegia) | 1 | 1 |
| Frontal abscess (clinical diagnosis) | 1 | 1 |
| Pontine haemorrhage | 1 | 1 |
| Total | 14 | 12 |

Of these 14 cases 9 are known to have had associated endocarditis.

In addition to these cases there were a further 8 patients in whom such diagnoses as 'acute mania', 'prolonged confusional state', 'cerebritis', etc. were made. Five of these 8 patients died.

*Antibiotic Sensitivity*

All staphylococci cultured were tested for sensitivity against a sulphonamide and the antibiotics. Phage typing was not performed. To show the changing pattern of antibiotic sensitivity, the 9 years, 1953 - 61, have been divided into 3 periods of 3 years each. The results are shown in Table II. This confirms that there has been the expected gradual increase in resistance throughout the 9 years. The figures for chloramphenicol are of interest. This drug held

TABLE II. ANTIMICROBIAL SENSITIVITY OF STAPHYLOCOCCI GROWN FROM BLOOD CULTURES DURING 1953-1961. ANALYSIS INTO THREE 3-YEAR PERIODS SHOWS THE CHANGING PATTERN. FIGURES REPRESENT PERCENTAGE OF ORGANISMS TESTED WHICH WERE SENSITIVE TO THE ANTIMICROBIAL AGENT IN QUESTION

| Period | Total tests | Sulphatriad % | Penicillin % | Streptomycin % | Chloramphenicol % | Tetracycline % | Erythromycin % | Novobiocin % | Kanamycin % | Neomycin % |
|---|---|---|---|---|---|---|---|---|---|---|
| 1953-1955 | 30 | 47 | 50 | 67 | 100 | 80 | 100* | | | |
| 1956-1958 | 42 | 24 | 26 | 60 | 98 | 64 | 82 | | | |
| 1959-1961† | 40 | 10 | 25 | 46 | 69 | 65 | 80 | 80 | 100* | 100* |

* Not quite every organism was tested against these antibiotics.
† During this period a few organisms were tested against vancomycin and methicillin. None was resistant.

pride of place for effectiveness during the first 2 periods, but during the third period it fell to being only slightly more effective than tetracycline. The reason for this is probably the great popularity which the drug has enjoyed in Groote Schuur Hospital. In this series it was used in more instances even than penicillin (78 *versus* 76). Erythromycin was used much less, probably explaining why it has remained more effective.

The emergence in hospitals of staphylococci insensitive to a number of antibiotics has led to the use of the term 'hospital' staphylococci. For purpose of discussion the term 'resistant' staphylococci is used here and arbitrarily defined as strains insensitive to 3 or more of the following drugs: Sulphatriad, penicillin G, streptomycin, chloramphenicol, tetracycline and erythromycin. The 112 cases in this series for which sensitivity results are available are distributed as follows:

| | Number | Deaths | Mortality % |
|---|---|---|---|
| 'Resistant' staphylococci | 51 | 31 | 61 |
| Other strains | 61 | 12 | 20 |

Of the 26 patients who acquired their infection inside hospital, all but 1 were infected with 'resistant' staphylococci and 17 of these patients died (mortality 65%). Among the 37 patients with acute osteitis only 4 'resistant' strains were cultured, while there were 10 among the 19 patients with septic abortions. In some of the prolonged cases in which positive blood cultures were obtained repeatedly, it was noted that resistance developed to one or more of the drugs used in treatment. This was an infrequent happening and appears actually not to have presented a therapeutic problem in any of the cases in this series.

*Acute Osteitis*

There were 39 patients with osteitis in the series. Two of these were adults in whom osteitis occurred incidentally during the course of staphylococcaemia. The remarks that follow apply to the remaining 37, in whom acute osteitis was the initial (and often the only) lesion.

Fig. 4 shows the ages of these patients; from this it is obvious that these 37 are a small section of a much larger group whose average age is well below 12 years. This

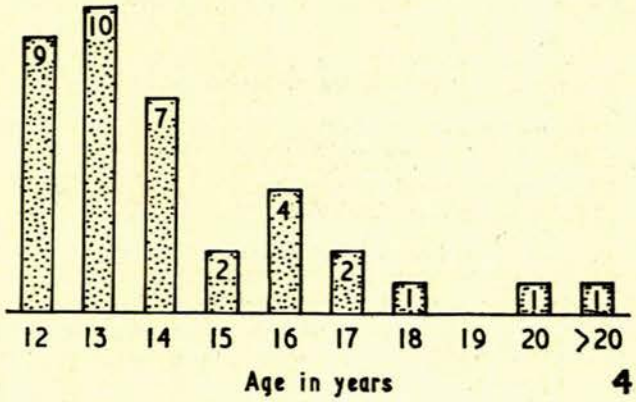


*Fig. 4.* Acute osteitis — age incidence.

whole group has been described by Shandling.[7] As he pointed out, Cape Town has by far the highest published incidence of acute osteitis in the world. The present figures bear this out.

Among the 37 patients there were only 6 whites, in keeping with the observation that acute osteitis is a disease of the poor.[8] The only death among the 37 was that of a white child, a girl of 12 years who was admitted with acute osteitis of a tibia. For various reasons (including a leucocyte count of 6,400 per c.mm. and a sedimentation rate of 4 mm. in the 1st hour) the diagnosis was missed and she was admitted initially to a medical ward. Surgical drainage was late and inadequate. Despite vigorous antibiotic therapy she developed endocarditis, and death was due to cerebral embolization.

A definite history of trauma affecting the site where osteitis subsequently developed was obtained from 12 patients. In 9 of the 37 more than one bone was affected. As mentioned above, only 4 of the patients were infected with 'resistant' organisms.

*Postabortal Cases*

Nineteen cases (17% of the total number) were associated with septic abortions. This appears to be a much higher

incidence than in any other reported series. As a group, these cases tended to be florid and severe, with multiple complications and protracted courses. However, the mortality figures are not as bad as might be expected:

| | *Number* | *Deaths* | *Mortality* % |
|---|---|---|---|
| Whites | 5 | 3 | 60 |
| Non-whites | 14 | 5 | 36 |
| Total | 19 | 8 | 42 |

Six of these patients admitted to mechanical interference, but it would seem likely that abortions resulting in staphylococcaemia are almost always criminally induced. It is of interest that more than half (53%) of these patients were infected with 'resistant' staphylococci.

*Cases Following Surgical Operations and Septic Intravenous Infusion Sites*

Under this heading there were 17 patients of whom 11 (65%) died. The responsible organism was a 'resistant' staphylococcus in all the 16 patients for whom sensitivity results are available; 14 of these patients had just had a surgical operation. In 4 it was noted that the wound was septic and in 5 that a drip site was infected. The majority of these patients were on antibiotic therapy from the time of their operations. The actual operations were:

Appendicectomy
Gastrectomy for gastric ulcer (2 cases)
Laparotomy for unexplained peritonitis
Cholecystectomy
Abdomino-perineal resection
Resection of strangulated small bowel with ileostomy
Splenectomy (thrombocytopenia)
Iliac artery embolectomy (mitral stenosis, renal failure)
Mitral valvuloplasty with baffel
Colporrhaphy
Vaginal radium insertion and cystoscopy
Cystoscopy and retrograde pyelogram
Transurethral resection of the prostate

In 3 cases staphylococcaemia appeared to originate from septic blood transfusion cut-down sites in patients who did not have operations.

About half the 17 patients in this group were critically ill or had serious underlying disease before they acquired staphylococcaemia; in some the staphylococcaemia was a terminal event. It is the remaining patients, those who come into hospital relatively well for surgical treatment of what are not necessarily fatal conditions, that are causing surgeons and hospital administrators such concern at present. These patients form a much lower proportion of all cases of staphylococcaemia in this series than in most published reports,[2,9] and the sinister relationship between prostatic surgery and staphylococcaemia noted in some reports[9-11] is not apparent here. The annual incidence of this form of staphylococcaemia has remained fairly constant in this series, in contrast to the frightening increase in some centres.[2,4]

*Subacute and Chronic Cases*

It is a well-known characteristic of the staphylococcus to localize in one or more sites and produce a picture of subacute or chronic pyaemia. Among the patients under review there were many who had prolonged stays in hospital. This is to be expected, for established staphylococcaemia, especially with endocarditis, is seldom cured by a short course of antibiotics. If one accepts that a clinical course longer than 12 weeks indicates a subacute or chronic stage of the disease, then there were 7 such cases. One patient was still developing metastatic abscesses 15 months after drainage of a breast abscess. One postoperative patient was finally cured of a chronic staphylococcal pyaemia after 14 months. The remaining 5 patients had clinical courses lasting between 4 and 8 months. Examination of the clinical records of these 8 patients shows no particular features in common apart from the duration of their illness. Two of them had endocarditis; 1 had a (secondary) lesion in bone; 2 are known to have died. Some of the patients with acute osteitis developed chronic lesions at the same site, but none developed chronic pyaemia.

TREATMENT

These patients were treated by many different clinicians in almost every department of the hospital, so it is not surprising that therapy was far from uniform. This and the fact that patients with severe and prolonged illness tended to be given many different antibiotics makes critical analysis very difficult.

It has been noted above that chloramphenicol was the most popular antibiotic, followed by penicillin. Most of the cured patients were treated by a combination of two or more antibiotics and all patients cured of endocarditis received a combination of drugs including at least one bactericidal antibiotic. In only one instance was a patient cured (or indeed was there a definite clinical response) by an antibiotic to which the organism was insensitive *in vitro*. This was a patient with severe, prolonged postabortal staphylococcaemia without endocarditis, from whom positive blood cultures were obtained on 8 separate occasions over 3 months. The organism was sensitive to tetracycline, chloramphenicol and erythromycin, but intensive treatment with these antibiotics had produced either temporary or inadequate response. Finally penicillin, to which the organism was repeatedly 'insensitive', was used in doses of 8 - 16 mega units daily for 31 days and appears to have cured the patient. Penicillin was used in this way on a few other occasions by clinicians who presumably felt that a high dose of a bactericidal drug should be tried (whatever the *in vitro* sensitivity) especially in cases of endocarditis.[12] On every other occasion it met with a notable lack of success.

Surgical drainage appeared to influence the course of the disease only in those patients with acute osteitis. In these the surgical policy of early thorough drainage (including drilling), combined with vigorous and prolonged antibiotic therapy, produced good results.[7] It is significant that the only patient with osteitis who died was one in whom the diagnosis was missed, so that surgical treatment was late and inadequate.

Other measures used in the cured patients are less easy to assess. Blood transfusions were required in all the prolonged cases and often produced a striking improvement in the patient's general condition. No patients were given antistaphylococcal serum, but a few received human gamma globulin. Steroids were given to 6 patients and in 3 of them it is felt that this drug may have tided them over a critical period long enough to be cured by antibiotics.

A study of the fatal cases shows that in 11 of them staphylococcaemia was a terminal complication of an already fatal disease. Among the other patients some died despite what would be considered early and adequate treatment. However, in an appreciable number of the fatal cases retrospective study suggests that the patients died either because of a delay in diagnosis, or because antibiotic therapy was inadequate in quantity or quality.

With regard to the delay in diagnosis, this series confirms that staphylococcaemia can present in many bizarre and confusing ways, making a diagnosis on clinical grounds very difficult on occasion. But the findings also show that adherence to the principle of investigating all patients with unexplained pyrexia by blood culture will eliminate undue delay in diagnosis, for no initial temperatures under 100°F. were recorded and in almost every instance the initial blood culture was positive. An occasional tragedy was failure to appreciate the significance of a positive blood culture. Inadequate antibiotic therapy included persistence with drugs after they had been shown to be ineffective *in vitro* and rapid switching of antibiotics if a quick response was not obtained. This series confirms the findings of Wilson and Hamburger[13] that staphylococcaemia is a prolonged illness and there may be a slow response to a drug combination which finally cures the patient. In fact positive blood cultures may still be obtained after the patient has, for a few days, been getting the antibiotics which finally cure him. *The most common error was stopping antibiotics too soon and allowing the patients to relapse.*

## CONCLUSIONS

The figures presented here show that Groote Schuur Hospital has an incidence and mortality rate for staphylococcaemia comparable with other centres.[2,10,13,14] Features which appear to be individual to this hospital are the high proportion of cases associated with acute osteitis and with septic abortions, and the relatively low proportion of infections acquired within the hospital. Otherwise the clinical and pathological features correspond with other descriptions.

The facility with which staphylococci grow in blood culture makes this a very effective method of diagnosis (only 3 cases diagnosed at autopsy had not had positive cultures). The fact that non-significant positive cultures are common is a strong indication for repeating initial cultures later the same day. The number of culture bottles in which growth occurs is of some assistance as a guide. The occurrence of a case of coagulase-negative *Staph. albus* endocarditis is a warning that this organism may on occasion become pathogenic. This is likely to occur in severely debilitated patients or following open-heart operations.[15]

The patients with osteitis form an interesting group for comparison with the others. Untreated osteitis carries the same sinister prognosis as other types of staphylococcaemia, so it is worth considering what factors enable the surgeons to save almost every patient with osteitis, while the mortality for the other groups remains about 50%. It is suggested that the difference is due to the following factors:

1. A dramatic clinical presentation enabling a very early diagnosis to be made.
2. Early effective surgical drainage.
3. A young group of patients with almost no complicating medical conditions (except, perhaps, malnutrition).
4. An aggressive antibiotic attack, the drugs being used in larger doses and for longer periods than is often the case with non-osteitis cases.

Analysis of the results of treatment enable certain conclusions to be drawn. Perhaps the most important single factor is speed of diagnosis. In a condition which may present a most confusing clinical picture this demands a high index of suspicion and early recourse to blood culture. Delay in diagnosis constantly involves the dangers of endocarditis and intracranial complications. Delayed treatment may eliminate the infection, only for the patient to die of structural damage (in this series 1 died from a ruptured mycotic aneurysm and 1 from mitral incompetence).

Antibiotic treatment must be prolonged; 4 weeks is perhaps the minimum duration, and this will often have to be extended.

Choice of antibiotics is obviously important in the treatment of staphylococcaemia. It has not yet been settled whether single or multiple drugs should be used for these cases, or whether treatment should include a bactericidal drug; meanwhile it would seem reasonable to give every patient the benefit of a combination of antibiotics, including a bactericidal drug. The distinction between bactericidal and bacteriostatic antibiotics is not clear-cut,[16] but as a rough working rule one could aim to give these patients 1 bactericidal drug from the group penicillin G, methicillin, vancomycin and kanamycin; and 1 bacteriostatic drug from the group erythromycin, tetracycline, chloramphenicol and novobiocin. The percentage of organisms sensitive to each of these drugs has been indicated in Table II (it is unlikely that strains resistant to vancomycin or methicillin will be encountered at this stage). Of the bactericidal drugs penicillin G in big doses remains the treatment of choice for the 25% of organisms sensitive to it. For the remaining 75% methicillin should be used. Frequent, painful injections are a drawback, but this drug is probably the sheet anchor of treatment at present. It should be used initially if sensitivity results are not available. Vancomycin and kanamycin are very effective, but toxic, alternatives for use in special circumstances.[16-18] Of the 4 bacteriostatic drugs mentioned, erythromycin would perhaps be first choice or, if the organism is insensitive to it, the alternatives, in descending order of safety, would be tetracycline, chloramphenicol, and novobiocin. For all aspects of the interrelationship between antibiotics and staphylococci the excellent studies of Petersdorf *et al.*[16] should be consulted.

Of the other methods of treatment available, timely blood transfusion is certainly important and steroid therapy in critically ill patients is probably worth trying. Recent experimental work by Lambert[19] suggested that gamma globulin is unlikely to have any effect on staphylococcal infections.

In general, patients with staphylococcaemia require very careful nursing and daily clinical observation. They may at any stage develop life-threatening complications affecting almost any system in the body.

## SUMMARY

A review has been undertaken of 114 patients with staphylococcal septicaemia and pyaemia treated at Groote Schuur Hospital over the past 9 years. Children under 12 years of age were excluded. The clinical and pathological features have been analysed, and the diagnosis and treatment of this condition are discussed. In general this

series differs from other reports in having a much higher incidence of acute osteitis and septic abortions, while the incidence of infections acquired within hospital is lower.

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