Papers and Originals

Cross-infection by *Pseudomonas aeruginosa* as a Hazard of Intensive Surgery

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Although cross-infection has always presented serious problems, there has within recent years been an increased awareness of the growing prevalence of Gram-negative organisms, especially *Pseudomonas aeruginosa,* as causes of serious morbidity in the hospital environment (Finland *et al.,* 1959 ; Williams *et al.,* 1960 ; Barber, 1961). A variety of factors appear to have contributed to this changing pattern of hospital-acquired bacterial infections, but the extensive use of broad-spectrum antibiotics, corticosteroids, and cytotoxic and immunosuppressive drugs, and the increased susceptibility of individuals subjected to advanced and intensive surgery or medical techniques, have been of major significance. In this context, infections by *Ps. aeruginosa,* an organism of low pathogenicity to healthy individuals, are likely to be particularly serious and associated with a high mortality. This opportunist has an inherently high resistance to most currently available antibiotics, and many antiseptics are less active against *Ps. aeruginosa* than against other vegetative bacteria.

Recently a series of *Ps. aeruginosa* infections of the respiratory tract occurred in a cardiovascular surgical unit involving seven patients, three of whom died. The three fatal cases had been subjected to open-heart surgery followed by intensive care, including tracheostomies and prolonged postoperative mechanical ventilation. They had also received corticosteroids, while all the cases had had prophylactic broad-spectrum antibiotic cover.

This paper describes the clinical and bacteriological features of the outbreak together with the epidemiological investigations and control measures which were undertaken.

History of the Initial Outbreak

During the two months December 1966 to February 1967 30 operations were performed in the unit. Twenty-two were mitral valvotomies or other short closed-heart procedures, and none of these showed any evidence of respiratory or wound infection. On the other hand, of the eight patients who underwent open-heart surgery with extracorporeal circulation, five developed respiratory tract infections due to *Ps. aeruginosa* and three of these subsequently died. The following is a synopsis of the postoperative course of the first five cases in which *Ps. aeruginosa* was isolated.

Case 1.—This patient's operation was for closure of an atrial septal defect. He was breathing spontaneously immediately after the operation, and subsequently his course was uneventful apart from a respiratory infection. Culture of his sputum on the fourth day grew *Escherichia coli* (sensitive to ampicillin, streptomycin, and tetracycline) and *Ps. aeruginosa* (sensitive to colistin only). The patient made a good recovery.

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Case 2.—An aortic valve (Starr) prosthesis was inserted in this man on 12 December, after which intermittent positive-pressure ventilation by Bennet's machine was required and a tracheostomy was performed two days later. *Ps. aeruginosa* was cultured from his bronchial aspirate during the subsequent 10 days, and he died of progressive respiratory insufficiency and septicaemia.

Case 3.—This boy had an operation for closure of an atrial septal defect on 19 January 1967 and required a tracheostomy for respiratory insufficiency on 21 January, and ventilation was assisted. Four days later *Ps. aeruginosa* was grown from specimens of tracheal aspiration and he died three weeks after operation.

Case 4.—Another operation for closure of an atrial septal defect took place on 2 February 1967. Though the postoperative course was uncomplicated by clinical evidence of infection, culture of sputum on the fifth day revealed *Ps. aeruginosa.* This was an isolated specimen, however, and subsequent cultures were negative. The patient made a good recovery.

Case 5.—An operation for replacement of the mitral valve was carried out on 6 February 1967. Tracheostomy was performed for respiratory insufficiency on 8 February and ventilation was assisted mechanically. Culture of tracheal secretions on each of the next three days showed a heavy growth of pseudomonads. Blood cultures on the fourth and fifth days also grew *Ps. aeruginosa.* The patient died on the sixth day after operation.

On reviewing the postoperative course of these cases, certain common factors emerge. It has been routine practice in this unit to administer ampicillin and methicillin by slow intravenous drip for seven days after open-heart surgery. Further, the three patients who died had received comparatively large doses of hydrocortisone (500 mg. six-hourly) throughout the first postoperative week in an effort to modify the "post-perfusion lung" syndrome. While the three patients who died were certainly the most ill from the point of view of their cardiovascular status, it might also be argued that the combination of the antibiotics used, together with continued large doses of hydrocortisone, rendered them unduly susceptible to an overwhelming infection by *Ps. aeruginosa.*

Bacteriological Investigations and Control

It will be noticed that all five cases had had tracheostomies. This operation is notorious for profoundly modifying respiration and so exposing the lung to pseudomonas infection (Dupont *et al.,* 1962), and this risk is much greater when the artificial airway has to be prolonged, as *Ps. aeruginosa* is about 10 times commoner in the secretions collected after a month than in those taken after a week (Tunevall, 1956). Moreover, all the cases had been given ampicillin and methicillin prophylactically, and *Ps. aeruginosa,* resistant to these antibiotics, was present in the sputa of all seven cases ; it was also found in the tracheostomy wounds of two of the fatal ones (Cases 2 and 5) and in the throat, bronchi, and blood of one (Case 5) at necropsy.

These findings suggested a respiratory source for the infection, and this was confirmed when random swabbing of the equipment of the theatre suite and adjacent rooms showed that at this stage isolation of pseudomonads was limited to the anaesthetic equipment, and in fact to the connecting tube of the Bennet ventilator and the Ambu rebreathing bag.

Wahba (1965) showed that by identifying the specific pyocines produced by the pseudomonads it was possible to distinguish different strains, and, using 12 such indicators, he differentiated eight strains. Gillies and Govan (1966), using only eight pyocine indicators, identified 36 types, of which Nos. 1, 3, 5, 6, and 9 comprised over 70% of all *Pseudomonas* strains they tested. With this technique Dr. Gillies was able to confirm that the strain of *Ps. aeruginosa* found in the ventilator and the Ambu bag was the relatively rare type 10 identical to that also found in the three fatal cases.

The respiratory equipment had come under suspicion after the second case. The Ambu bag was destroyed and sterilization of the ventilator attempted by washing with chlorhexidine digluconate followed by exposure to ethylene oxide by running the gas through the machine. Solutions of chlorhexidine have recently been incriminated in the actual spread of pseudomonads in a hospital (*Brit. med. J.*, 1967 ; Burdon and Whitby, 1967). The last three of these five cases were infected by *Ps. aeruginosa* after the anaesthetic equipment had been treated by both methods before use in each case. Clearly these methods of disinfection were ineffective. Moreover, the organism had by now contaminated the distilled water in the nebulizer of the Bennet ventilator and also the alternative Barnet ventilator, the connecting tube being again implicated as well as the flowmeter, which was found to contain blood clotted on the vanes when dismantled.

Pseudomonas aeruginosa was recovered from the throat swabs of 6 of the 50 staff and patients, and it was suspected that the organism, which would not normally be a commensal in this site, had become widely disseminated.

For our earlier isolations of pseudomonads we had relied on the selective medium of Lowbury and Collins (1955) which employs 0.03% cetrimide ; and to eliminate *Klebsiella* and *Proteus* spp., which also survive, we had depended on pseudomonal colonies giving a positive oxidase test, rather than the improved fluorescence of the organism which Brown and Lowbury (1965) achieved by modifying the medium. As it was intended to culture numerous swabs from the theatre and surroundings, the cetrimide plates were made even more selective by adding 5 μg. of nalidixic acid per ml. This was based on a clinical trial (Barlow, 1963) in which 24 out of 25 strains of *Pseudomonas* had resisted nalidixic acid inhibitory to *Klebsiella* and *Proteus* spp. in cultures of urine. Experiments showed that our *Ps. aeruginosa* type 10 could just survive these combined inhibitory agents, which together excluded other bacteria.

Several hundred moistened swabs were now used to sample the flora on the fittings and equipment of the theatre and adjoining rooms. *Ps. aeruginosa* was isolated from the following relatively inaccessible places even after the use of various disinfectants, which had included glutaraldehyde, and chlorhexidine with cetrimide: ventilator of ceiling light ; ventilator louver on wall ; panel of air-conditioning control on wall ; trap and gauge of suction apparatus on wall ; corrugated tubing of Boyle's anaesthetic apparatus ; sampling tube and undersurface of chassis of Astrup blood-gas analysis trolley ; grids on drains of floor and sink ; a pair of clogs ; and in adjacent rooms the *x*-ray camera, and the drains of the dark-room, ward, and sluice.

It was obvious that there was particularly widespread contamination with *Pseudomonas* sp., and it had to be assumed that nothing short of their complete eradication would ensure elimination of the risk from the epidemic of type 10. A solution of activated glutaraldehyde has been recommended by Rittenbury and Hench (1965) for sterilizing anaesthetic equipment such as masks, suction catheters, and endotracheal tubes ; but Ross (1966) found that at a concentration of 50% this compound required between 15 and 30 minutes to kill pseudomonads in broth, and that with added blood even this was insufficient. It is problematic whether any disinfectant can be relied on with gross contamination with blood, but the timely appearance of a new disinfectant Portex-DCR containing dipenidam which was reputedly active against pseudomonads enabled us to test this agent, using a broth culture of the type 10 organism and a similar broth culture with 10% blood added. The results showed that Portex-DCR killed the pseudomonads in two minutes at a dilution of 1/160 in broth, but that in the presence of blood 1/40 was the effective dilution. This agent offers two further advantages: it is non-irritant in effective dilutions ; and it changes colour from green to blue when no longer active—this indicator is a useful guide under circumstances where the solution is being applied by lay staff such as cleaners.

The unit was closed and the six nurses with positive throat cultures were sent on a week's leave. Intricate equipment was dismantled, cleaned, and then sterilized by 24 hours' exposure to ethylene oxide in plastic bags ; but all other appliances and the rooms themselves were disinfected by washing with 1/40 Portex-DCR. As this still left surviving pseudomonads, notably in the drains and the Astrup blood-gas analysis apparatus, this washing was repeated with 1/20 Portex-DCR, and lysol was poured down the drains. Pipes and ducts were flushed for 30 minutes with Trilene to remove oil deposits. It was found, however, that the organism survived 25 minutes' exposure to this detergent, and therefore the Trilene was followed by washing with Portex-DCR 1/20. Two months elapsed before complete clearance was reached for all equipment and personnel, some equipment having to be dismantled by the makers to dislodge an organism described as "notorious for its ability to survive in unlikely situations" (*Lancet*, 1961).

Reappearance of Infection—Cases 6 and 7

On 15 May 1967 a housewife (Case 6) who had been admitted for mitral valve replacement produced a purulent sputum infected with *Ps. aeruginosa* type 10, raising doubts whether disinfection had been effective. Inquiry showed, however, that she had been in the ward during the first half of December 1966, when she would have encountered the infection and might well have harboured it since. Colistin was added to her prophylactic methicillin and ampicillin, and the sputum was cleared of pseumonads after a week, though not before a patient in the adjoining bed (Case 7) had shown transient cross-infection. Closure of an atrial septal defect on this man 10 days previously had necessitated a tracheostomy, and on 15 May 20 colonies of *Ps. aeruginosa* were isolated from his tracheal secretions on a single occasion. Colistin methanesulphonate 1.5 mega units eight-hourly was given for three days and there was no recurrence.

Discussion

The distinction between pathogenic bacteria and harmless saphrophytes, traditional since the days of Koch, has become blurred in recent years, and a survey at Boston City Hospital (Finland *et al.*, 1959) showed that between 1935 and 1957 intestinal commensals had progressively replaced the pyogenic cocci isolated from cases of bacteraemia. Moreover, the analysis disclosed that before 1941 *E. coli* alone was responsible but that after that date *Klebsiella, Proteus,* and *Pseudomonas* spp. increased in frequency. Secondary infection of wounds by *Ps. aeruginosa* has long been recognized because it will often colour the pus, and as skin and nasal carriers are relatively rare in contrast to those bearing staphylococci (Barber, 1961 ;

Williams *et al.*, 1966) cross-infection from other cases had to be assumed. Indeed, Selwyn *et al.* (1964), investigating 1,231 cases of hospital infection in Edinburgh, found that no less than 70% were non-staphylococcal, and they concluded that there had been comparative neglect of the role of these other organisms and especially of "coliform bacilli," including *Ps. aeruginosa.*

Opportunists such as these, though normally less invasive than the pyogenic cocci, are also far less fastidious in growth, so that their destruction is a formidable challenge to both antiseptics and antibiotics. Two ecological hazards are inseparable from the use of antibiotics. One is the emergence of resistant mutants, which has already become a major problem with the hospital staphylococcus; the other is disturbance of the diversity of bacterial flora. With "broad-spectrum" antibiotics only the hardier organisms will survive, and *Pseudomonas* is perhaps the hardiest of all. Widespread and even autochthonous, this organism is essentially a saphrophyte and its normal habitat in man is limited to the intestine, and even in this situation its presence is exceptional (Lowbury and Fox, 1954).

Although human susceptibility to *Ps. aeruginosa* has been shown by random serological tests (Jones and Lowbury, 1965) to be very variable, certain groups would seem to be gravely at risk. Ayliffe *et al.* (1965) attributed cases of meningitis and urinary and wound infections in a neurosurgical unit to preoperative use of a shaving brush infected with *Ps. aeruginosa,* and similarly contaminated eye-drops accounted for pseudomonal infection of 15 out of 25 ophthalmic operations, in six of which there was loss of the eye (Ayliffe *et al.*, 1966).

Phillips and Spencer (1965), who described 10 medical cases of respiratory infection with *Ps. pyocyanea,* four of which were fatal, noted that, ordinarily, the organism is virtually absent from human sputum, not one of 347 routine samples containing pseudomonads. Eight of their cases were infected like ours by a ventilator, two being cross-infections in adjoining beds, and they noted the role of prophylactic antibiotics, tracheostomy, and corticosteroids also in predisposing to infection.

In the present series of eight cases one or other of these three factors (corticosteroids, broad-spectrum antibiotics, and tracheostomy) again played a part, and in the three fatal cases all were present.

Though *Pseudomonas* sp. were found distributed in inaccessible sites ranging from the ceiling light to the drains the infections were primarily respiratory, and the fortunate chance of a relatively uncommon pyocine type being involved clearly implicated the ventilator and the rebreathing bag.

That droplet and dust-borne infections may not in practice be a risk from other sources was confirmed by experiment. While the theatre was closed 18 settle-plates were exposed for an hour on the floor and fittings. For 10 minutes of this time a surgeon, anaesthetist, and four nurses wearing masks and gowns talked and moved about the theatre, being asked to locate the plates. Notwithstanding that two of the team had positive nose or throat swabs for *Ps. aeruginosa* and that these organisms still persisted on the floor grid to the drains, no pseudomonads settled on the plates. We believe that carriers play little part in an epidemic of pseudomonal infection, but that even a single major case, especially respiratory, may contaminate the entire environment to such a degree that eradication becomes very difficult indeed.

Cetrimide-nalidixic acid plates and pyocine typing were found to be valuable tools in tracing the source and mode of spread of pseudomonads, just as modern disinfectants were needed for the control. Portex-DCR 2% proved to be the disinfectant most effective against *Ps. aeruginosa,* acting even in the presence of blood, unlike its rivals, though up to 10% was necessary in vitro in the presence of gross contamination. This was supplemented by ethylene oxide fumigation of electrical and other intricate equipment and by Trilene irrigation for ducts. No disinfectant is likely to succeed, however, in the eradication of pseudomonads that are being harboured in blood-clot and other protein debris; and, as Phillips and Spencer (1965) found, there is still need for a practical filter to protect anaesthetic equipment. Such a filter would need to have really easy access to disposable pads so that they could be replaced constantly as they became sodden. In the absence of such filters we raised the Barnet ventilator to a level above the patient's head to minimize the contamination of the apparatus by gravity. Expedients suggested by others have been to place a filter on the intake tube of the ventilator (Bishop *et al.*, 1963) or to put chlorhexidine in its humidifier unit (Phillips and Spencer, 1965); but none of these precautions deals with what is probably the prime source of infection, the patient himself who originally infected the machine.

There may be an additional argument here for adding colistin to the prophylactic antibiotics recommended for cases on intensive care, but its nephrotoxicity must be borne in mind. There are certainly good grounds for monitoring the sputum of all such cases on admission and before and after operation. By using cetrimide-nalidixic acid plates we were able to screen heavy inocula, and we felt well justified when this procedure detected *Ps. aeruginosa* in the respiratory tracts of the last two cases. It showed that it is possible to get early warning of what might have become recrudescence of infection by this most formidable organism.

Summary

An outbreak of respiratory infection in a cardiac surgery unit affected seven cases, with three deaths. *Pseudomonas aeruginosa* type 10, the causative organism, was also isolated from the anaesthetic equipment.

Possible predisposing factors were tracheostomy, corticosteroids, and prophylactic antibiotics.

Measures taken to prevent a recurrence included screening of sputa on a selective medium and the use of an efficient new antiseptic containing dipenidam.

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