

SEPTICEMIA CAUSED BY PSEUDOMONAS AERUGINOSA

A Review

James W. Sayre, M. D. *

On February 1, 1963, a tragic airplane accident took place in the Ulus district of Ankara. Many people were killed directly and about 65 were hospitalized in various Ankara hospitals. The Hacettepe Medical Center received and cared for 29 patients, of whom a total of fourteen died. A majority of those dying did so within 24 hours from burns of 30 - 95 per cent of the body surface with deep tissue involvement. However, of those who survived to their third day, blood cultures were drawn on fourteen patients. From six of these pyocyaneus (*Pseudomonas aeruginosa*) was grown. These patients were at that time receiving «prophylactic» antibiotics, consisting of penicillin and streptomycin, in hopes of averting the inevitable infection that accompanies burns of large areas of body surface. Of these six patients, five later died of the pseudomonas bloodstream infection or complications attributable thereto. It is for the purpose of obtaining a better understanding of this highly lethal infection that the present review has been made.

Pseudomonas aeruginosa (Pyocyaneus) was first recognized as a pathogenic organism in 1890, by Charrin. It is widely distributed in nature, being found in air, water, the human gastrointestinal tract and normal human skin. Its almost universal presence makes it a continuously potential pathogen in infections of man. It is a commonly observed pathogen in surgical infections and its presence is often made known by a characteristic blue - green pus. Like *Aerobacter aerogenes* and *Proteus*, it is one of the gram-negative organisms which in recent years has been receiving increasing attention in both the medical and surgical fields for a number of reasons, which will be reviewed in some detail here. Mortality rates from the septicemia form of this infection are high, and, as yet, antimicrobial therapy is not adequate in its eradication.

Incidence of Ps. aeruginosa. Finland (1) comments on the apparent rise in incidence of this organism in blood stream infections in a study of blood culture results obtained at Boston City Hospital

* Consultant pediatrician, Hacettepe Medical Center, Ankara.

in the 22 years that have elapsed during the antibiotic era. In 1935 there was only one bacteremia caused by this organism; in 1957 there were twenty. The same situation was also noted in the occurrence of other gram - negative organisms: *E. coli*, *Aerobacter aerogenes* and *Proteus*, as well as hemolytic *Staphylococcus*. Yow, (2) in 1952, found a relative increase in the incidence of *Proteus* and *Pseudomonas* infections, noting 28 infections caused by these organisms occurring in patients receiving antimicrobial therapy. Among leukemic patients, Forkner (3) noted a striking susceptibility to this infection, its presence accounting for the death of patients second only to hemolytic *Staphylococcus*. In burned victims, Markley (4) describes 34 patients (all of whom died), with *Pseudomonas* septicemia which developed after receiving prophylactic penicillin. In none of these patients were cultures positive until at least 48 hours after the occurrence of the burn.

Source of this infection. Unlike the hemolytic *Staphylococcus* which is commonly carried by normal people in the nose, this organism is more often isolated from the gastrointestinal tract, and to a lesser degree, from the skin. To some extent the organism may be more commonly found in the nose and on the skin of personnel caring for burned patients. Lowbury (5) found 94 per cent of dust samples contaminated on burned wards, 86 per cent of air samples during wound dressings, and 27 per cent while bedding was being changed. Sandusky (6) discovered this organism to be present in local anesthetic solutions, suction bottles, connecting tubing, and on anesthetic masks, the last after chemical sterilization. Altemeier (7) describes the unfortunate occurrence of eight cases of *Pyocyanus* meningitis caused by the introduction of contaminated spinal catheters for diagnostic or therapeutic procedures. These catheters had been soaked in a «sterilizing solution» for periods up to three weeks and he noted the difficulty of killing these organisms in solutions ordinarily employed to sterilize at room temperature.

Conditioning and predisposing factors. In an excellent review of the subject, Curtin (8) points out that *Ps. aeruginosa* sepsis is not an infection which occurs in the healthy, otherwise well, individual, but one which almost always has some kind of predisposing «Achilles' heel». He groups these into four categories, as follows :

1. Premature infants. All eighteen infants which he describes had birth weights below 2,000 grams. Three survived. Many had diarrhea, infected cords or skin lesions and several demonstrated

«ecthyma gangraenosum» (described below). In many this organism was thought to be a terminal invader, acting only as a contributor to the demise of the patient.

2. Children with congenital or acquired diseases. In this group of 28, one survived. Predisposing conditions were : cystic fibrosis, Hirschsprung's disease, sickle cell anemia, meningocele, congenital heart disease, nephrosis, malignancy treated with anti-metabolites, and osteomyelitis under therapy with antibiotics.
3. Patients with leukemia. Fifteen of this group of 25 patients were children. Nearly all the patients were already on steroids, anti-metabolite drugs or antibiotics which were, in a way, «keeping alive a sick horse,» at the same time modifying or weakening the host. In several the occurrence of a remission from the leukemia was accompanied by a bacterial remission from this infection. Portals of entry could be found in many cases and included: skin, gastrointestinal tract and respiratory tract. Skin lesions tended to be deep ulcerated areas with little reaction or pus in the tissues.
4. Adults with debilitating disease. In this group of eighteen patients, the median age was 60 and all but three were over 50. Accompanying diseases were: urinary tract, eight; diabetes, two; gout and previous gastrectomy, one each. In this group eight patients died. Of those who died, many had been receiving X-ray therapy, nitrogen mustard therapy, or steroids.

In a similar study of five cases which occurred at various times within one year in the same hospital, Williams (9) points out that in all these cases there were predisposing factors: leukemia, two cases; steroid therapy, two cases; drug-induced agranulocytosis, one case; and that these patients all contracted their infection while in hospital. He also points out the striking increase in isolations of *Ps. aeruginosa* from sputums of other patients on the same wards, during this same period. He feels it very likely that the organism became almost a resident on the wards at the time, attacking most severely those who were most susceptible for the reasons outlined above.

Burn cases. These deserve special consideration with respect to predisposing factors inasmuch as here one is usually dealing with a previously healthy individual who has not been receiving drugs or radiotherapy. His local and systemic defense mechanisms are intact at the time the injury is sustained. However, deep tissue burns natu-

rally expose large areas of the body to microbial agents, shock may complicate the acute period, and body protein depletion occurring later often delays healing and thus prolongs the period of potential exposure to large numbers of bacteria. The first 48 hours after burning are very seldom complicated by infection. Death more often occurs as a result of blood or fluid loss, shock or cerebral anoxia. After this time bacteremia may be detected and its complications arise. Balch (10) made careful studies on burned patients with respect to the following: 1. Leukocyte - plasma bactericidal effect; 2. Plasma bactericidal effect; 3. Serum hemolytic complement. In respect to these modalities he found that humoral protective mechanisms remained essentially intact throughout the entire post-burn period. In fact, in the first three to four days, they were often at higher-than-normal levels. However, when he studied the local tissue response, results were more revealing. By scarifying a small area of intact skin, removing superficial layers of epithelium, he studied the subsequent migration of leukocytes to the area. Massive infiltration of leukocytes seen normally after such a procedure was also observed to take place in the initial three to four days after burning. However, the same test performed on burned patients after the first three to four days demonstrated a progressive loss of this response to abrasion. Balch suggests this may be due to some change in vascular response brought about by burning, but other, perhaps, more complicated, mechanisms may be involved. Certainly the susceptibility to *Ps. aeruginosa* septicemia in burns has some host factors in addition to the obvious fact that a large microbial population inhabits necrotic human tissue at ideal incubator temperatures with large venous beds open to bacterial invasion.

The role of antibiotics in the pathogenesis of Pseudomonas infections. Although much careful study and thought has been given to this subject it is still a very intensely debated problem. Curtin (8) has the following to say: «It is now well recognized that the normal microflora of the human body maintains an important balance that in some way deters invasion by pathogens. This balance can be altered by antibiotic therapy, particularly by the so-called broad-spectrum coverage, which eliminates susceptible commensals and leads to unbridled multiplications of resistant 'saprophytic' species. In this situation, 'superinfection' by drug resistant bacteria becomes likely. Prominent among the survivors are the *Pseudomonas* bacilli.» That a prompt change in bacterial flora occurs during antimicrobial therapy can be easily attested by the frequency with which cul-

tures gram-negative bacilli or «resistant *Staphylococcus aureus*» from the throat of any patient who has been receiving penicillin, erythromycin or any broad - spectrum antibiotic for two days or more. For the patient with a short-term, not-too-serious illness this very seldom presents any problems. However, for the patient whose illness is of a chronic debilitating nature and who has one or more of the complicating or predisposing factors mentioned above, the problem can become a large one, indeed.

Clinical features. There are a few distinguishing features of this bacterial infection, although it is seldom possible to suspect it on purely clinical grounds. High fever is a fairly consistent finding. Since this infection is best classified as a «super - infection», it is more usual to suspect it as a cause of secondary rise in fever after a few days or weeks in hospital. «Bacterial shock» is a fairly common occurrence, manifested by sudden collapse, coma and hypotension. Two types of skin lesions have been described. The first and more common, known as «ecthyma gangraenosum», begins as a vesicle containing an opalescent liquid which soon ruptures and develops into a hemorrhagic, necrotic ulcer. These lesions are characteristically not purulent. In the burned series of Markley (4) this lesion antedated death by 24 to 48 hours, and always appeared to carry a severe prognosis. It seems to occur more commonly among children. The second lesion described by Markley is a tender subcutaneous nodule with surrounding erythema which does not break down. This lesion was not so quickly followed by death. Two patients were observed with this lesion among the *Ps. aeruginosa* septicemia burned victims at Hacettepe. From the laboratory point of view, it is thought by some (8) that leukopenia is a feature, but this is certainly not characteristic and may only reflect a change in host resistance brought about by the predisposing factors mentioned above. Pathological changes seen at autopsy are characteristic, however, and may be seen grossly. They consist in hemorrhagic infarcted areas found most commonly in the bowel mucosa, kidney, lungs and heart.

Treatment. To date, no wholly satisfactory antimicrobial agent has been found. Although local infections in the skin and external ear can to some extent be controlled through local applications of Polymixin or Neomycin, or both, widespread lesions such as those seen in burns present problems because of the high cost of the drugs and the presence of fibrinous exudate and eschar preventing access to organisms. *Pseudomonas* possesses a high degree of sensitivity to

Polymixin in vitro (94 per cent of strains tested by Sandusky (6) were sensitive), although clinical results and mortality rates do not seem to bear this out. The organism does not seem to have the capacity to develop increased drug resistance, such as seen in the *Staphylococcus*. Jackson, (11) in 1951, could find no evidence of increase in bacterial resistance. Polymixin, however, does have the unfortunate disadvantage of nephro- and neuro- toxicity, necessitating limitation of its use to five to seven days and frequent observation of renal function. A newer drug, Colimycin (colistin sulfate), discovered in Japan and introduced in 1950, seems to possess all of the virtues of Polymixin with a high in vitro sensitivity, and is thought not to have the disadvantages of Polymixin. Meleney (12) observed no side effects in its use in the cases he treated. According to the information given in the prospectus of this drug, nephrotoxicity may be observed if there is pre-existing renal disease. However, present indications are that this drug may be used over longer periods with greater safety than can Polymixin.

Prevention. Since there is good reason to suspect that this is frequently a hospital - acquired infection, and that once acquired it is difficult to eradicate, one should look to ways of preventing its spread, particularly to the more susceptible patients. The following measures may be effective:

1. Look carefully for the patient whose antibiotic therapy appears to have been completed satisfactorily and stop drug therapy promptly, thus allowing a normal bacterial flora to re-establish itself in the respiratory and gastrointestinal epithelium. This in itself should keep down the number of patients harboring the pyocyanous organism.
2. Exercise great caution when handling patients with open, chronic wounds who remain in hospital more than a week. Pyocyanous, as well as the hemolytic *Staphylococcus*, may be grown from 35 to 50 per cent of these wounds.
3. The chronic debilitated patient, particularly in those groups mentioned above, is one who should be handled with «reverse precautions» to prevent his becoming infected. Such patients should not, if at all possible, be in close proximity to burned patients, septicemia patients, or patients with open wounds.
4. Perhaps most important to remember is that poor aseptic precautions or isolation techniques are almost never concealed under the umbrella of broad-spectrum antibiotic therapy.

Summary

A discussion of the causes, incidence and treatment of *Pseudomonas aeruginosa*, with emphasis on its relation to antibiotic therapy and predisposing factors. Special attention is focused on *Ps. aeruginosa* septicemia in burn cases. Preventive measures are suggested as a means of reducing this hospital-acquired infection.

REFERENCES

1. Finland, M., Jones, W.F.Jr., and Barnes, M.W.: Occurrence of serious bacterial infections since introduction of antibacterial agents, *J.A.M.A.* 170: 2188, 1959.
2. Yow, E.M.: Development of proteus and pseudomonas infections during antibiotic therapy, *J.A.M.A.* 149: 1184, 1952.
3. Forkner, C.E.Jr., Frei, E., Edgcomb, J.H., and Utz, J.P.: *Pseudomonas* septicemia - Observations on twenty-three cases, *Am. J. Med.* 25: 877, 1958.
4. Markley, K.: Fatal *Pseudomonas* septicemia in burned patients, *Ann. Surg.* 145: 175, 1957.
5. Lowbury, E. J. L., and Fox, J.: Epidemiology of infection with *Pseudomonas pyocyanea* in burns unit, *J. Hyg.* 52: 403, 1954 (Quoted by Barber).
6. Sandusky, W. R.: *Pseudomonas* infections: Sources and cultural data in a general hospital with particular reference to surgical infections, *Ann. Surg.* 153: 996, 1961.
7. Altmeier: In discussion of the paper by Sandusky above, p. 1004.
8. Curtin, J. A., Petersdorf, R. G., and Bennet, I. L. Jr.: *Pseudomonas* bacteremia: Review of ninety-one cases, *Ann. Intern. Med.* 54: 1077, 1961.
9. Williams, R., Williams, E. D., and Hyams, D. E.: Cross-infection with *Pseudomonas pyocyanea*, *Lancet* 1: 376, 1960.
10. Balch, H. H., Watters, M., and Kelley, D.: Resistance to infection in burned patients, *Ann. Surg.* 157: 1, 1963.
11. Jackson, D. M., Lowbury, E. J. L., and Toplay, E.: *Pseudomonas pyocyanea* in burns; its role as pathogen, and value of local Polymixin therapy, *Lancet* 2: 137, 1951.
12. Meleney, F. L., and Prout, G. R. Jr.: Some laboratory clinical observations on Colymycin (colistin) with particular reference to *Pseudomonas* infections, *Surg. Gynec. Obstet.* 112: 211, 1961.
13. Barber, M.: Hospital infection yesterday and today, *J. Clin. Path.* 14: 2, 1961.
14. Colebrock, L., Duncan, J. M., and Dallas Ross, W. P.: Control of infection in burns, *Lancet* 1: 893, 1948.