SEPTICAEMIA DUE TO GRAM-NEGATIVE BACILLI

A Report of Two Cases

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SINCE the beginning of the antibiotic era there have been reports of increased frequency of bacteraemia and other serious infections due to gram-negative bacilli.

Reports have appeared mainly in the American literature. Waisbren (1951) gave an account of 29 cases of bacteraemia due to gram-negative bacilli, Spittel, Martin, Wellmann and Geraci (1954) reviewed 65 cases of *E. coli* bacteraemia, and Spittel, Martin and Nichols (1956) reported 137 cases occurring in a period of 15 years.

Finland, Jones and Barnes (1959) quoted 30 deaths annually from *E. coli* septicaemia at Boston City Hospital since 1953. This report focused attention on the magnitude of the problem, drew editorial comment in the *British Medical Journal* (1960) and was cited by Barber (1961) in a recent survey of hospital infection. Few cases, however, have been reported in this country. A search of the British literature of the last 13 years, covering the period of increasing use of antibiotics, yielded only three accounts. Single cases were reported by Librach (1954) and Williams (1960). Three cases were mentioned by Williams, Williams and Hyams (1960), although only one of these gave positive blood cultures.

Price (1956) states that *Bacterium coli* septicaemia is rare unless it occurs as a terminal event, in which case it is not at all uncommon. Burrows (1959) agrees that it is very rare, except as an agonal invasion in acute infective processes. Dubos (1958) only mentions that colon bacilli may gain access to the blood stream, particularly in infants, in the agonal stage of diseases and immediately after death.

Although the use of antibiotics in America has been more widespread and indiscriminate than in this country, the contrast between the large number of cases reported in America and the almost complete lack of such reports in Britain is striking.

It is felt, therefore, that the cases described

here, of bacteraemia neither transient nor agonal may be of interest.

Case 1

The patient, a woman aged 40 years, presented with a three week history of nausea, vague abdominal discomfort and frequent vomiting. On admission she was pale and thin and showed slight cyanosis with conjunctival icterus but no generalised jaundice. The abdomen was soft and the liver was tender, its edge palpable four finger breadths beneath the right costal margin. The spleen and kidneys could not be felt. After admission the patient continued to run a high swinging temperature (see Fig. 1) and she developed abdominal distension and marked right-sided tenderness with almost board-like rigidity.

Blood cultures taken on the 7th, 8th, 9th and 11th days yielded a gram-negative bacillus. The organism, identified as *Paracolobactrum coliforme*, was sensitive to chloramphenicol, streptomycin and furaltadone, but resistant to penicillin, erythromycin and the tetracyclines. The urine contained albumin, red cells, pus cells and bacteria, but no sugar. A coliform bacillus was recovered but this organism was not the same as that found in the blood or later at autopsy. Agglutination reactions for Typhoid, Paratyphoid A and B and Brucellosis were negative. Treatment was begun with chloramphenicol, 0.5 g. t.i.d., on the 9th day and four days later 1.0 g. streptomycin daily was added. Although at first there was no clinical improvement, by the 22nd day the abdominal distension and tenderness had diminished and a blood culture at this time was negative. Nevertheless, the swinging pyrexia continued and in view of this furaltadone 0.5 g. t.i.d. was substituted for the chloramphenicol. On the following day the temperature dropped dramatically and there was a short spell of clinical improvement before her condition again deteriorated. She died 31 days after admission and 24 days after her first positive blood culture. Before her death her blood urea had risen to 150 mg./100 ml. and terminally there was a very severe hyperchloraemic acidosis.

At autopsy, soft enlarged mesenteric glands were found, filled with creamy pus. The small bowel was diffusely injected but not ulcerated. The histological appearances did not justify a diagnosis of acute enteritis. Multiple liver abscesses were found (Fig. 2) but there was no microscopic evidence of a pre-existing cirrhosis. The portal vein appeared recently thrombosed.

The capsules of the kidneys were thickened and adherent and the outer surfaces were rough and scarred. On section, thinning of the cortex was obvious and

FIG. 1.—Case 1. Course of illness, with antibiotic therapy.

FIG. 2.—Case 1. A section of the liver showing multiple small abscesses.

multiple pale areas were distributed throughout both kidneys. A bilateral necrotising papillitis was found as well as severe chronic pyelonephritis. The pelves, ureters and urinary bladder appeared healthy and no abscesses were present.

Case 2

The patient, a man aged 37 years, sustained multiple injuries in the collapse of a building. These included

dislocation of the hip, fracture of thigh and pelvis, splitting of the scrotum with extrusion of both testes and rupture of the bladder with bleeding into the retro-pubic space. The fractures and dislocation were reduced and a hip spica applied. The bladder wall was closed around a de Pezzer catheter, and a Foley catheter was inserted *per urethram*.

Recovery from his bone and joint injuries was slow but uneventful, but his urinary tract continued to give

FIG. 3.—Case 2. Course of illness, with antibiotic therapy.

trouble. Six months after the accident his condition was still poor. Although the suprapubic wound was dry there was induration along the urethra and tender swellings were present in the scrotum and perineum. Urine was passing *per urethram* but also leaking through a mid-line perineal sinus. He complained of dysuria and pain in the right loin and he was febrile. X-ray at this time revealed multiple calculi in the right kidney.

Following this his general condition deteriorated further, his pyrexia increased, and he experienced frequent rigors (Fig. 3). Agglutination reactions for Typhoid, Paratyphoid A and B and Brucellosis were negative but his urine and blood each yielded a heavy growth of a coliform bacillus and *B. proteus*. The coliform was sensitive to furaltadone but resistant to penicillin, erythromycin, chloramphenicol, the tetracyclines, streptomycin and sulphonamide. The proteus was sensitive to furaltadone and chloramphenicol.

Furaltadone 250 mg. q.i.d. and chloramphenicol 250 mg. q.i.d. were given and rigors ceased after the second day of treatment, although the patient remained febrile. After a week the chloramphenicol was discontinued and the dose of furaltadone increased to 500 mg. q.i.d. His temperature quickly fell to normal and he was very much improved. No growth was obtained from blood culture at this time. Since his urinary infection was persisting, nitrofurantoin—the nitrofur derivative most effective in the urinary tract—was introduced in doses of 100 mg. t.i.d. and the furaltadone was reduced to 250 mg. q.i.d.

Following this a transfusion of two pints of blood was given and the patient's condition continued to improve. His blood culture remained sterile and the urinary flora changed to a light mixed growth. He was allowed up and twenty days after his first positive blood culture he was transferred to a convalescent hospital.

Discussion

In cases of bacteraemia due to gram-negative

bacilli consideration should be given to the presence of any recognizable portal of entry and to possible predisposing factors.

In the series of 137 patients studied by Spittel and others (1956) bacteraemia was considered to be the result of spread from the genito-urinary tract in 60% of cases, from the gastro-intestinal tract in 25%, and in 15% the source was unrecognized. These authors stress that in more than half the cases where the portal of entry has been identified operative interference has preceded the bacteraemia. Felty and Keefer (1924) and Waisbren (1951) agree that the genito-urinary tract is the most frequent source of spread, and the latter author mentions that the commonest precipitating factors are catheterization and instrumentation.

In Waisbren's series of 29 cases four had evidence of liver disease. Whipple and Harris (1950) record four cases of *E. coli* septicæmia in Laennec's cirrhosis of the liver. They consider that the deficiency of effective reticulo-endothelium in cirrhotic tissue or the changes of the hepatic circulation may account for the apparent increase in susceptibility. Four of Spittel's 137 cases had hepatic cirrhosis. In the same series 14 patients had diabetes mellitus, a not unexpected proportion in view of the diabetic's well-recognized predisposition to any form of infection.

The cases recorded here are of septicæmia occurring in adults as a protracted illness and not as an agonal invasion. In neither case was there

clinical or laboratory evidence of diabetes mellitus or hepatic cirrhosis.

In the first case the gastro-intestinal tract and the urinary tract are the two portals of entry of the organism to be considered. The presence of chronic pyelonephritis suggests that the urinary tract had been infected for a considerable time. A coliform bacillus was isolated from the urine at the same time as the first positive blood culture was obtained, but the two organisms were not identical. The necrotizing papillitis is considered at least partly responsible for this patient's death. Both Allen (1952) and Anderson (1957) are of the opinion that it is most commonly found associated with severe acute ascending pyelonephritis in diabetics, and in non-diabetics it is usually associated with urinary tract obstruction. In this patient neither of these factors pertained, although there was chronic renal disease. It is interesting to note that necrotizing papillitis is recorded as an associated condition in one of the fatal cases of *E. coli* septicæmia described by Spittel and others (1956).

Although the serosal aspect of the bowel showed a patchy fibrinous exudate, histological examination revealed only mild inflammatory changes in the mucosa. Consequently it is felt that the alimentary tract was a less likely source of origin of the septicæmia.

In the second case, in view of the infection associated with the trauma, the repeated catheterization and the presence of multiple renal calculi there seems little doubt that the septicæmia resulted from spread from the urinary tract. This theory would appear to be confirmed by the

similarity of the organisms isolated from both the blood and the urine.

With regard to the use of furaltadone, Sadusk (1956) recorded the disappearance of bacteræmia due to *E. coli* on the administration of this drug when other antibiotics had failed. In the cases now reported a negative blood culture was obtained in Case 1 after treatment with chloramphenicol and streptomycin, but it was only after the use of furaltadone that the striking fall in temperature occurred. In the second case only furaltadone (of the commonly used antibiotics) was active *in vitro* against both the organisms isolated. It proved effective clinically, sterilized the blood and, together with nitrofurantoin, produced considerable improvement in the urinary infection. None of the toxic manifestations described by American writers and quoted in the *British Medical Journal* (1961) was noted in either case.

Summary

1. Two cases of septicæmia due to gram-negative bacilli are reported. Each occurred in an adult as a protracted illness and not simply as an agonal invasion. One case yielded a *Paracolobactrum coliforme* and survived for 24 days after the first positive blood culture. The other patient, who gave a mixed growth of *B. proteus* and a coliform bacillus, made a satisfactory recovery.

2. Furaltadone was used in treatment and its possible value in such cases is mentioned.

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REFERENCES

- ALLEN, A. C. (1952): 'The Kidney,' p. 348. London: J. and A. Churchill.
- ANDERSON, W. A. D. (1957): 'Pathology,' 3rd edition, p. 569. London: Henry Kimpton.
- BARBER, MARY (1961): Hospital Infection Yesterday and Today, *J. Clin. Path.*, **14**, 2.
- BRITISH MEDICAL JOURNAL (1960): Leading article, **1**, 43.
- (1961): Leading article, **1**, 264.
- BURROWS, W. (1959): 'Textbook of Microbiology,' 17th edition, p. 463. London: W. B. Saunders.
- DUBOS, R. J. (1958): 'Bacterial and Mycotic Infections of Man,' 3rd edition, p. 368. London: Pitman.
- FELTY, A. R., and KEEFER, C. S. (1924): A Clinical Study of Twenty-eight Cases of Blood Stream Infection by the Colon Bacillus, *J. Amer. med. Ass.*, **82**, 1430.
- FINLAND, M., JONES, W. F., and BARNES, MILDRED W. (1959): Occurrence of Serious Bacterial Infections since Introduction of Antibacterial Agents, *Ibid.*, **170**, 2188.
- LIBRACH, I. M. (1954): *B. Fæcalis Alkaligenes* Infections with a Report of a Case of Septicæmia, *Postgrad. med. J.*, **30**, 424.
- PRICE, F. W. (1956): 'Textbook of the Practice of Medicine,' 9th edition, p. 97. London: Oxford University Press.
- SADUSK, J. F. JR. (1956): Nitrofurantoin in Treatment of Coliform Bacteræmia; Report of a Case, *Calif. Med.*, **84**, 117.
- SPITTEL, J. A., JR., MARTIN, W. J., WELLMANN, W. E., and GERACI, J. E. (1954): Bacteræmia owing to *Escherichia Coli*; A Review of 65 Cases, *Proc. Mayo Clinic*, **29**, 447.
- , —, and NICHOLS, D. R. (1956): Bacteræmia owing to Gram-negative Bacilli; Experiences in the Treatment of 137 Patients in a 15-year Period, *Ann. intern. Med.*, **44**, 302.
- WAISBREN, B. A. (1951): Bacteræmia due to Gram-negative Bacilli other than the *Salmonella*, *A.M.A. Arch. intern. Med.*, **88**, 467.
- WHIPPLE, R. L., and HARRIS, J. F. (1950): *B. Coli* Septicæmia in Laennec's Cirrhosis of the Liver, *Ann. intern. Med.*, **33**, 462.
- WILLIAMS, E. (1960): Septicæmia caused by an Organism resembling *Pasteurella Septica* after a Dog Bite, *Brit. med. J.*, **ii**, 1926.
- WILLIAMS, R., WILLIAMS, E. D., and HYAMS, D. E. (1960): Cross Infection with *Pseudomonas Pyocyanea*, *Lancet*, **i**, 376.