# Severe clinical conditions associated with *Bacillus cereus* and the apparent involvement of exotoxins

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SUMMARY    Twenty-one cases of infection with *Bacillus cereus* are summarised. The histories supplied showed that at least 15 of these were associated with severe or potentially severe symptoms including two deaths. Analysis of the production of exotoxins, including haemolysin and phospholipase, by these strains is given, and the relevance of these metabolites to the severity of the condition is discussed. Three incidents of bovine mastitis resulting from *B. cereus* and involving three deaths are also included.

The observations presented here together with those of previous reports which are reviewed indicate that *B. cereus* may be of clinical importance, not just as an opportunist but also as an agent of potentially severe infections in its own right.

The predominant interest in *Bacillus cereus* over the past decade has been from the standpoint of its role in food poisoning. However, the association of this organism with clinical conditions not related to food and often severe in nature has been pointed out from time to time for many years. Despite this, hospital microbiologists often readily admit that they frequently see the organism but almost invariably dismiss it as unimportant.

Contributing to the lack of appreciation of the potential pathogenicity of *B. cereus* was the uncertain taxonomy of the species before the 1950s. Although the specific name *B. cereus* was applied to a pathogenic blood culture isolate as early as 1937 (Clarke), up to about 1950 the organism, as far as can be established (Gibson and Gordon, 1974), was sometimes grouped with various other species under *B. subtilis* (Weinstein and Colburn, 1950), sometimes under *B. anthracoides* (or just 'anthracoids') of which it was probably the predominant member, and sometimes under what were probably more specific names, *B. subtilis mycoides*, *B. siamensis*, *B. anthracis similis*, and *B. pseudoanthracis*.

Under one or other of these names, or even less specifically, simply 'aerobic spore bearer' (ASB), it is likely that *B. cereus* was the organism associated with numerous clinical manifestations. In papers

on this subject, Heaslip (1941), Weinstein and Colburn (1950), Farrar (1963), and Goepfert *et al.* (1972) cite some 20 reports between 1898 and 1937 in which organisms under these names were associated with abscess formation, severe eye infections, meningitis, kidney and urinary tract infections, puerperal sepsis, pulmonary infections, septicaemias, and war wounds. ASBs also featured in war wounds of the second world war (Spooner, 1941), and clinicians today who were practising at that time testify to the severity of war wounds infected with anthracoids.

Classification of the species under the name *B. cereus* was fully established in 1952 (Smith *et al.*), and under this name the organism has continued to be recorded as the cause of bacteraemia and septicaemia (Curtis *et al.*, 1967; Crowley, 1970; Leffert *et al.*, 1970; Coonrod *et al.*, 1971; Goullet and Pépin, 1974; Raphael and Donaghue, 1976; Barnham and Taylor, 1977; Chastel *et al.*, 1977), pneumonia and pleurisy (Stopler *et al.*, 1964; LeLourd *et al.*, 1967; Coonrod *et al.*, 1971; Feldman and Pearson, 1974; Leff *et al.*, 1977), endocarditis (Craig *et al.*, 1974; Block *et al.*, 1978), gas gangrene-like infections (Gröschel *et al.*, 1976; Turnbull *et al.*, 1977a), meningitis (Leffert *et al.*, 1970; Raphael and Donaghue, 1976), cerebral necrosis (Turnbull *et al.*, 1977a), middle-ear infection (Lázár and Jurecsák, 1966), osteomyelitis (Solny *et al.*, 1977), and urinary

tract infection (Melles *et al.*, 1969).

References to severe *B. cereus* infections in domestic animals are also readily obtainable, especially with respect to gangrenous mastitis in cattle (Jasper *et al.*, 1972; Wohlgemuth *et al.*, 1972).

As a result of the role of this organism in food poisoning, the Food Hygiene Laboratory has become a centre of reference for *B. cereus* and in the past two years has begun to receive increasing numbers of isolates from clinical cases not related to food. With a concurrent development of our knowledge of exotoxin production within the species, an interesting picture is emerging in which the extent of production of specific toxin activities by an isolate appears to be related to the severity of the condition.

## Methods

### ISOLATES EXAMINED

The strains and their isolation histories are sum-

marised in Table 1. Five of these derived from countries outside the British Isles. All were routinely confirmed biochemically as *B. cereus*, and their serotypes were determined (Taylor and Gilbert, 1975). A number of these strains have featured in previous publications, as indicated in Table 1.

### TOXIN TESTS

Nine-hour cultures of the organisms in Brain-Heart Infusion Broth (Difco) containing 0·1% glucose (BHIG) shaken at approximately 100 cycles/min at 36°C were centrifuged and filtered.

For vascular permeability reaction, including skin necrosis tests (VPR), 0·05 ml of cell-free filtrates was inoculated intradermally in duplicate into the shaved backs of two adult rabbits. At 3 hours postinoculation approximately 4 ml of 2% Evans Blue dye was injected intravenously, and measurements of blueing and necrosis were made after a further hour.

For rabbit intestinal necrosis reactions the cell-free filtrates were concentrated four-to seven-fold and

Table 1   *Association of* Bacillus cereus *and its exotoxins\* with severe infection*

| ** Ref Strain | Serotype | Clinical condition/source | Recorded indications of severity | VPR (mm) Total | VPR (mm) Necrosis | RINR | MLT | HL titre | PL (mm) |
|---|---|---|---|---|---|---|---|---|---|
| 667-71/78 | 2 | Postoperative wound | Gangrenous | 20·5 | 2·8 | 4+ | + | 4 | 4·4 |
| ¹837/76 | 17 | Postoperative wound | Not available | 20·2 | 3·3 | 4+ | + | 40 | 8·0 |
| 615/78 | 14 | Stab wound | Septic | 19·9 | 2·0 | 2+ | + | 40 | 5·8 |
| 2808-10/77 | 6 | Blood culture (and CSF***) | Infant born very oedematous; developed purulent meningitis | 17·0 | 1·7 | 3+ | + | 160 | 5·9 |
| ¹841/76 | 11 | Umbilical swab | Not available | 16·2 | 1·6 | 3+ | + | 40 | 3·5 |
| 2682/77 | NT | Blood culture | 10-month child; acute diarrhoea and vomiting for 48 h | 16·1 | 1·8 | 1+ | + | 80 | 5·8 |
| 30/76 | NT | Lymph node biopsy | Not available | 15·6 | 1·3 | 2+ | + | 20 | 4·8 |
| 660/78 | 20 | Facial burns | Cellulitis developed | 15·2 | 1·0 | 3+ | + | 20 | 4·8 |
| ¹,³,²2141/74 | 11 | Cerebral and respiratory tract necrosis | Died (infant) | 13·9 | 0·5 | 2+ | + | 160 | 6·0 |
| ⁴3562/77 | 8 | Blood culture | High fever | 13·7 | 1·2 | 3+ | + | 2 | 1·8 |
| 1820/77 | 8 | Bovine mastitis | Died | 12·4 | 0·3 | ± | + | 160 | 7·5 |
| 1419/77 | 12 | Bovine mastitis | 2 cows died | 11·9 | 0·1 | − | + | 320 | 6·0 |
| 1414/77 | 12 | | | 2·8 | 0 | − | + | 80 | 5·8 |
| 1589/77 | 12 | | | 4·9 | 0 | − | ± | 80 | 6·0 |
| 1047/78 | NT | Panophthalmitis | Vitreous body destroyed | 11·7 | 1·0 | 1+ | + | 160 | 5·3 |
| 2724/77 | NT | Lung abscess | Died | 11·4 | 0·2 | 3+ | + | 80 | 3·8 |
| ³⁴4581B/76 | 22 | Postoperative wound | Gangrenous | 11·2 | 0 | 2+ | + | 320 | 2·3 |
| 4581A/76 | 22 | | | 5·3 | 0 | − | − | 80 | 2·5 |
| 659/78 | NT | Ascitic fluid; lymphoma patient | Uncertain relevance | 11·2 | 0·1 | − | + | 20 | 4·5 |
| 1046/78 | NT | Panophthalmitis | Vitreous body destroyed | 10·4 | 0 | − | + | 2 | 5·5 |
| 941B/78 | 10 | Renal dialysis machine and water supply | Pyrexia after dialysis | 10·1 | 2·4 | − | + | 320 | 3·3 |
| 941A/78 | 10 | | | 8·6 | 0 | − | ± | 320 | 6·5 |
| 969,70/78 | NT | Postoperative wound | Severe | 9·6 | 1·3 | 2+ | + | 30 | 5·9 |
| 968,71/78 | 21 | | | 10·0 | 0 | ± | + | 40 | 4·8 |
| ¹838/76 | NT | Antral washout | Not available | 9·6 | 0 | ± | ± | 160 | 2·5 |
| ¹,⁵836/76 | 2 | Blood culture | No severe effect | 9·0 | 0 | ± | − | 80 | 8·8 |
| 928/78 | NT | Amputation stump | Septic | 8·6 | 0 | − | + | 8 | 2·5 |
| 624/76 | 12 | Bovine mastitis | Not available | 6·3 | 0·4 | − | + | 80 | 7·5 |
| 2040/78 | NT | Rejection site of replaced severed arm | No toxic reaction or clear involvement of the bacteria in the rejection | 5·6 | 0 | n | + | <2 | 4·5 |
| 2039/78 | NT | | | 3·0 | 0 | n | + | <2 | 8·0 |
| 2038/78 | NT | | | 0 | 0 | n | + | <2 | 6·0 |

VPR = vascular permeability reaction; RINR = rabbit intestinal necrosis reaction; MLT = mouse lethal test; HL = haemolysin; PL = phospholipase. **¹ Turnbull *et al.* (1977b); ² Turnbull *et al.* (1977a); ³ Turnbull (1976); ⁴ Chaslel *et al.* (1977); ⁵ Barnham and Taylor (1977). ***Culture was not available. NT = not typable. n = not done.

injected into ligated rabbit intestines, and the results were recorded as previously described (Turnbull *et al.*, 1977b).

For mouse lethal tests, 0·5 ml of the unconcentrated cell-free filtrates was injected into the tail veins of duplicate adult mice and the mice were observed for 45 minutes.

Haemolysin titrations were carried out according to the method of Johnson and Bonventre (1967) using two-fold serial dilutions of culture supernatants incubated with 0·5% rabbit erythrocytes in 0·85% saline.

Phospholipase activities were determined as the mean radii of zones of opacity forming after 20 hours at 36°C around duplicate 5 mm wells in an egg-yolk-mannitol based agar containing 50 $\mu$l of the cell-free filtrate.

## Results and Discussion

The toxin profiles of the isolates are given in Table 1. The strains are listed in order of decreasing VPR, which is an established measure of exotoxins of microorganisms which increase the permeability of cutaneous blood vessels to plasma proteins at the site of injection (Craig, 1971). In the case of *B. cereus*, high levels of production of this toxin result additionally in development of necrosis within a few minutes. The total reaction is the sum of the mean radii (in millimetres) of the zones of light and dark blueing and, when present, necrosis. Although given to the first decimal place for the convenience of placing the strains in order, the values should not be interpreted too precisely and can vary by two or three units on repeated testing; this reflects not only animal to animal differences but also some variations in other factors such as growth of the organisms from batch to batch of BHIG.

In a study on production of this toxin by 116 strains of *B. cereus* from a wide variety of sources (Turnbull *et al.*, 1979), it was found that the strains could be conveniently placed, on the basis of total VPR, into five categories: (1) 0-4·9; (2) 5·0-9·9; (3) 10·0-14·9; (4) 15·0-19·9; (5) 20·0-24·9. For the purposes of general interpretation, categories 4 and 5 represent strong production of the toxin, 2 and 3 intermediate production, and 1 weak production. Since only about 7·5% of *B. cereus* strains so far tested fall into category 1, it is presumed that the majority of strains are potentially capable of causing severe effects under the appropriate circumstances of infection.

In 19 of the 24 cases listed in Table 1, *B. cereus* strains of categories 3, 4, and 5 were isolated. On five occasions more than one strain of *B. cereus* was isolated from a single case; in four of these, one of

the variants showed an apparently greater ability to produce this toxin than the others and was presumed to be of predominant importance in the infection. In the fifth case (strains 2038-40/78), the low toxigenicity of all isolates from the rejection site correlated well with the clinical opinions expressed that, on the basis of an absence of gross necrosis, gas formation or foci of Gram-positive organisms in the rejected portion of the arm, and the absence of a toxic reaction in the patient, *B. cereus* was not responsible for the rejection. Strain 841/76 was found to elaborate this toxin more strongly than had previously been observed (Turnbull *et al.*, 1977b).

If every *B. cereus* isolation in a hospital laboratory was uncritically recorded, it would be difficult to distinguish those causally associated from those incidentally associated with clinical conditions. However, the probability that the implicated strains listed in Table 1 did have active roles in their respective cases is increased by the fact that, at the present time, this organism is generally regarded as having little clinical significance. It is likely, therefore, that, with the exception of strains 2038-40/78, where it was stated otherwise, only strains that drew attention to themselves either in being sole isolates or through their repeated isolation or by their predominance, would have been forwarded to the Food Hygiene Laboratory for further examination. These criteria should continue to be kept in mind in attempts to assess the relevance of *B. cereus* isolations from infections.

In nine of the cases (including the bovine mastitis), it was categorically stated that *B. cereus* was isolated in pure culture, and this was implied in a further two cases. In two more cases it was the only organism consistently isolated on several occasions, and in another two cases it was recorded as the only organism of possible significance. Other organisms of possible significance were reported in five cases, and the information was not available in the remaining four.

Correlation between VPR readings and the degree of necrotic damage qualitatively assessed in the rabbit intestinal necrosis model is good at the high and low levels of toxin production; there is some variance at intermediate levels, but this is as anticipated in animal tests for which there are limits to the extent of repetition that is feasible.

Mouse lethality is the longest standing pathogenicity test used for *B. cereus*. The role in severe human infections of the toxins that kill mice is also conjectural. Using fractions of BHIG culture filtrates partially purified by flat-bed electrofocusing, Turnbull *et al.* (1979) have obtained evidence that there are two lethal factors, one closely associated

Table 2 *Antibiotic sensitivity patterns in the 39* Bacillus cereus *isolates of Table 1*

| No. strains tested | 5 µg erythromycin | | | 1 unit penicillin G | | | 10 µg tetracycline | | | 10 µg gentamicin | | | 25 µg cephaloridine | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | I | R | S | I | R | S | I | R | S | I | R | S | I | R |
| 39 | 36 | 3 | 0 | *1 | 3 | 35 | 33 | 4 | 2 | 39 | 0 | 0 | *1 | 38 | 0 |

S = sensitive, I = intermediate; R = resistant; * 3562/77

with the rabbit intestinal necrosis reaction and its associated VPR factors and a second which is quite distinct and is associated with a haemolysin.

The haemolysin and phospholipase activities have also been viewed in the past as having a possible role in the pathogenic action of *B. cereus.* Wide variations in general haemolytic or phospholipolytic activities were obtained among the strains tested; in the case of haemolysins, there is clearly no relationship between titre and pathogenicity. The nature and interrelationships of the haemolysin, phospholipase, and lethal activity are reviewed elsewhere (Johnson and Bonventre, 1967; Bonventre and Johnson, 1970; Spira and Goepfert, 1975).

Pathogenicity studies on *B. cereus* and related organisms are numerous; the earlier ones were primarily concerned with differentiating *B. anthracis* from *B. cereus.* Studies relevant to this report are covered by other authors (Grierson, 1928; Burdon *et al.,* 1967; Stamatin and Anghelesco, 1969; Stretton and Bulman, 1975).

The distribution of serotypes is of interest in that, of those represented in these cases, only types 8 and 17 are at all commonly encountered in the Food Hygiene Laboratory.

Both the references reviewed and the findings presented here suggest that *B. cereus* may cause serious infections other than those of a gastro-intestinal nature and that such infections are possibly occurring throughout the world more frequently than is appreciated. In many of the cases listed, the patients were reported to have responded favourably to the appropriate antibiotic therapy, but it is also seen that lethalities can occur in both man and animals. Table 2 gives the antibiotic patterns in a disc diffusion sensitivity test using the Oxford strain of *Staphylococcus aureus* (NCTC 6571) as the control and the Stokes (1968) method of interpretation.

The toxin responsible for the purulent and necrotic nature of many *B. cereus* infections appears to be closely related or identical with the toxin responsible for the diarrhoeal-type syndrome associated with this organism, and some characterisation of this toxin has been achieved (Turnbull *et al.,* 1979).

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