Neonatal necrotising enterocolitis

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SUMMARY Five cases of neonatal necrotising enterocolitis occurred in full-term infants at Kingston Hospital in the space of 15 months. In all cases only the colon was involved. The pathological findings are discussed particularly in relation to the aetiology of the disease.

Neonatal necrotising enterocolitis (NNE) is a serious and often fatal disorder of unknown aetiology most commonly affecting premature infants who have undergone a form of stress such as hypoxia (Hopkins et al., 1970). The disease is characterised clinically by gastric retention, bile-stained vomiting, abdominal distension, and usually diarrhoea with blood in the stools within a few days of birth. Radiographic examination of the abdomen reveals gas within the bowel wall or inside the peritoneal cavity (Santulli et al., 1975).

The following is a description of five infants, each of whom had a partial colectomy for NNE at this hospital between December 1976 and February 1978 with emphasis on the pathological findings discussed in relation to the aetiology.

Case reports

Case 1
A 27-year-old para 1 + 1, blood group A negative, was artificially induced at 37 weeks' gestation because of a high titre of Rhesus antibodies. Induction was performed by rupture of the membranes and an intravenous syntocin drip. Because of failure to progress and a fetal heart rate of 40/min, a lower segment Caesarean section was done.

A male infant weighing 2650 g was delivered and the Apgar score at 1 minute was 2. Endotracheal intubation and artificial ventilation were performed. Spontaneous respiration did not begin until 4 minutes after birth. The baby appeared slightly jaundiced, and a direct Coombs' test on cord blood was positive. An exchange transfusion via an umbilical vein catheter was started but soon had to be discontinued (55 ml in, 80 ml out) as the baby developed congestive cardiac failure. After treatment the circulatory condition improved but jaundice became more obvious, and 70 hours after birth a successful transfusion of A negative blood was completed (370 ml in, 389 ml out). The baby remained well until 116 hours when a small amount of blood was passed per rectum. The infant, however, looked well, and abdominal examination revealed no abnormality. The stools were still bloodstained at 145 hours after birth, and at 170 hours the abdomen appeared distended. A plain abdominal x-ray showed pneumatosis coli and a diagnosis of NNE was made. Laparotomy was performed at 180 hours, at which time the large bowel from the caecum to the rectum was haemorrhagic and soft with a small number of perforations. A subtotal colectomy and ileostomy were performed and the baby made a good recovery from the operation. However, three weeks later he developed a Gram-negative sepsicaemia and died.

A postmortem examination showed no abnormality of the remaining bowel.

Case 2
A 26-year-old para 3 + 0 was delivered normally at 38 weeks' gestation of a female baby weighing 3670 g after spontaneous labour. The Apgar score at 1 minute was 9. The infant was fed with a standard milk formula (SMF) and progress was normal until 47 hours after birth when some blood and mucin were passed per rectum. At this time the baby appeared otherwise well with normal bowel sounds, but a plain x-ray of the abdomen suggested pneumatosis coli; 51 hours after birth the abdomen became distended. Gastric suction was performed and the baby was given 10% dextrose at a rate of 12 ml per hour through an intravenous umbilical catheter. However the infant continued to pass blood per rectum and developed bouts of abdominal colic. X-rays of the abdomen showed definite pneumatosis coli. A
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laparotomy was performed 68 hours after birth, at which time the ascending transverse and descending colon appeared dilated and haemorrhagic. The abnormal segment of bowel was removed and an end-to-end anastomosis of the terminal ileum to the sigmoid colon was done. Intravenous feeding was maintained for one week postoperatively when oral foods were gradually added. The baby made a good postoperative recovery.

CASE 3
A 27-year-old para 2 + 0 was induced at 38 weeks' gestation because of mild pre-eclamptic toxemia, and a female infant weighing 3000 g was delivered normally. The Apgar score at 1 minute was 8. Feeding was with SMF and the infant progressed normally for several days. However, 144 hours after birth some blood was noted in the stools although the baby looked well. At 168 hours the blood in the stools became more marked, and x-ray of the abdomen showed pneumatosis of the descending colon. Obstructive bowel sounds were heard 3 hours later, and a laparotomy was performed at 174 hours after birth. At operation the large bowel appeared normal from the caecum to the mid-sigmoid area but was not obviously inflamed or haemorrhagic. A subtotal colectomy and end-to-end anastomosis of the ileum to the mid-sigmoid was performed. Stool culture at this time grew an enteropathic Escherichia coli type 018AC. Stools sent for electron microscopy showed no virus particles. The baby made a good recovery.

CASE 4
A 26-year-old para 1 + 1 was induced at 39 weeks' gestation by rupture of the membranes and an intravenous infusion of syntocin over 6 hours. A Caesarean section was performed because of evidence of fetal distress. A male infant weighing 3750 g was delivered and was slow to establish respiration; the Apgar score at 1 minute was 4. The baby remained cyanosed for 5 minutes after birth and bradycardia was observed. Subsequently the baby seemed restless and hypertonic and was treated with phenobarbitone. Subsequent progress was good, the baby being fed with SMF until 65 hours after birth when traces of blood and mucin were noted in the stools. A plain x-ray of the abdomen showed only distended small intestine. The baby, however, began to pass more obvious blood per rectum and was started on intravenous fluids. At 76 hours pneumatosis coli was demonstrable radiologically, and a laparotomy was performed 2 hours later, at which time the whole colon appeared abnormal with obvious gas in the subserosa and mesentery. The rectum and sigmoid colon did not appear severely involved, and an end-to-end anastomosis of the ileum to mid-sigmoid colon was performed. The baby made a good recovery from the operation and one week later oral feeding was reintroduced.

CASE 5
A 27-year-old primipara went into labour spontaneously and had a forceps delivery of a male infant weighing 4055 g. The baby appeared normal and the Apgar score at 1 minute was 9. Feeding was started with SMF and the baby progressed normally until 80 hours after birth when blood and mucin were seen in the stools. The abdomen was slightly distended, and a few hours later pneumatosis coli maximal in the transverse colon was demonstrable radiologically. At 87 hours laparotomy was performed at which time the ascending transverse and descending colon were found to be thickened and haemorrhagic. A swab from the lumen of the affected bowel taken at operation grew only Bacteroides sp. A segment of large bowel from caecum to descending colon was removed, and an end-to-end anastomosis of the terminal ileum to sigmoid colon was performed. Postoperatively the baby made a good recovery.

A summary of the major clinical features is shown (Table).

Pathology

MACROSCOPIC APPEARANCE
Five specimens were received consisting of a few centimetres of terminal ileum and a variable length

Table Summary of clinical features in the five cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Mother's age (yr)</th>
<th>Parity</th>
<th>Gestation (weeks)</th>
<th>Induced</th>
<th>Mode of delivery</th>
<th>Sex</th>
<th>Weight at birth (g)</th>
<th>Apgar score at 1 min.</th>
<th>Onset of symptoms (hours after birth)</th>
<th>Operation (hours after birth)</th>
<th>Type of feeding</th>
<th>IV umbilical catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>1 + 1</td>
<td>37</td>
<td>Yes</td>
<td>Caesarean</td>
<td>M</td>
<td>2650</td>
<td>2</td>
<td>116</td>
<td>180</td>
<td>SMF</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>3 + 0</td>
<td>38</td>
<td>No</td>
<td>Vaginal</td>
<td>F</td>
<td>3670</td>
<td>9</td>
<td>47</td>
<td>68</td>
<td>SMF</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>2 + 0</td>
<td>38</td>
<td>Yes</td>
<td>Caesarean</td>
<td>M</td>
<td>3000</td>
<td>8</td>
<td>144</td>
<td>174</td>
<td>SMF</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>1 + 1</td>
<td>39</td>
<td>Yes</td>
<td>Caesarean</td>
<td>M</td>
<td>3750</td>
<td>4</td>
<td>65</td>
<td>78</td>
<td>SMF</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>0 + 0</td>
<td>39</td>
<td>No</td>
<td>Vaginal</td>
<td>M</td>
<td>4055</td>
<td>9</td>
<td>80</td>
<td>87</td>
<td>SMF</td>
<td>No</td>
</tr>
</tbody>
</table>
of large intestine. Common features to all specimens were marked vascular congestion and thickening of the bowel wall. The serosa in cases 1 and 5 was covered by a fibrinous exudate, and in the former, small perforations were present in the bowel wall. All the specimens with the exception of case 3 showed extensive mucosal ulceration, and much of the non-ulcerated mucosa had a cobblestone appearance. Case 3 appeared the least affected specimen, showing focal vascular congestion, slight mural thickening, and no mucosal ulceration. Numerous small submucosal cyst-like spaces were present in all the specimens and varied in size from being barely visible in case 3 to 3 mm maximum dimension in case 1 (Figs 1 and 2).

MICROSCOPIC FEATURES

The microscopic features varied even within the same specimen. Features common to all were marked vascular congestion, oedema, some focal haemorrhages, a variable inflammatory infiltrate, and the presence of cyst-like spaces in the submucosa (Fig. 3). The walls of these spaces were composed mainly of condensed connective tissue stroma (Fig. 4) although a small number had a partial lining of flattened cells (Fig. 5). Small cyst-like spaces were present in some serosal lymph nodes (Fig. 6). Sections of blocks from all specimens showed extensive mucosal necrosis with the exception of case 3, in whom the mucosa was largely intact (Fig. 7) but did show occasional foci of superficial necrosis (Fig. 8). Multinucleated giant cells were also present in case 3, being confined to the submucosa mainly beneath the muscularis mucosae (Fig. 9), although some multinucleated cells were present in the serosa of case 1. The inflammatory infiltrate in all cases was mixed, consisting of lymphocytes, neutrophils, plasma cells, histiocytes, and occasional mast cells. Eosinophils were prominent in all sections, existing singly and in clusters.

The inflammatory infiltrate was most marked in the submucosa but was present in lesser amounts in the muscularis propria and serosa. Neutrophils, and particularly eosinophils, were present in the smaller cyst-like spaces beneath the muscularis mucosae. Microthrombi were present in some of the smaller submucosal blood vessels in the severely inflamed areas but were not a prominent feature. Sections from case 3 showed a moderate increase of reticulin in the submucosa. Ganglion cells were normally distributed in sections from all specimens. Stains for
Fig. 3  Section of colon showing mucosal necrosis and cyst-like spaces in submucosa. Haematoxylin and eosin × 40

Fig. 4  Submucosa showing cyst-like spaces. H and E × 125
Fig. 5  Submucosal cyst-like space with partial lining of flattened cells. H and E × 230

Fig. 6  Subserosal lymph node containing cyst-like spaces. Sims-van Gieson × 125
Fig. 7  Case 3. Intact mucosa. H and E × 38

Fig. 8  Case 3. Focus of superficial mucosal ulceration. H and E × 125
organisms showed moderate numbers of Gram-positive rods on the surface and inside the necrotic mucosa of all specimens (Fig. 10). No organisms were seen inside most of the cyst-like spaces although an occasional Gram-positive rod was present in a small number of spaces in cases 1 and 2.

The terminal ileum in all cases appeared normal even when the caecum was severely inflamed. The lower cut ends of the specimens in cases 3, 4, and 5 showed submucosal pneumatosis, a feature that did not seem to affect postoperative recovery.

**Discussion**

At Kingston Hospital there has been a greater readiness to perform surgery on babies with NNE than in most centres with the view that early resection of the diseased segment of bowel, or as much of it as possible, would promote a quicker recovery from the illness, remove the chances of superadded infection, and reduce the incidence of stricture formation as a late complication. Because of this aggressive approach to the disease it is possible that we have been seeing the disease process in some of its developmental stages. NNE may affect any part of the small or large bowel, and, in contrast to other reports (Hopkins et al., 1970; Stevenson et al., 1971; Dudgeon et al., 1973; Santulli et al., 1975) where, in most cases, the small intestine was also involved, in our cases the disease process stopped at the ileocaecal valve.

The aetiology of NNE remains unknown but a variety of causes has been suggested. Low birth weight is a commonly associated factor, and premature infants form the majority of cases in the reported larger series (Stevenson et al., 1971; Dudgeon et al., 1973; Frantz et al., 1975). However, not all these instances concerned infants of low birth weight, and although prematurity may render an infant more susceptible to NNE it is not always a factor: all our babies were full-term deliveries and the smallest weighed 2650 g at birth.

All our infants were fed with SMF, and it is possible that enteric feeding may play a part in causation, but NNE can apparently develop in the non-fed infant and in those fed hyperosmolar and isosmolar formulae (Barrington, 1975). Pitt (1975) described experiments on a split litter of newborn rats subjected to oral contamination by a single strain of klebsiella. Some were suckled by their mothers and the others were fed simulated rat milk; all underwent a period of hypoxia for a period of 3 to 5 minutes each day. The rats that had been fed simulated rat milk formula died at 2 to 5 days of age, and postmortem examination of the bowel showed the appearances of necrotising enterocolitis. Those that had been suckled by their mothers did not develop the disease, and the bowels of these rats, which were sacrificed on the sixth day, were normal. Control groups fed formula or suckled with and without klebsiella contamination were not subjected to hypoxia and remained healthy. Pitt concluded that fresh rat milk, which contains large numbers of cells the majority of which are lipid-laden mono-

**Fig. 9** Case 3. Giant cells in submucosa. H and E × 345
nuclear cells, is protective against the disease, whereas the simulated rat milk formula, which contained no viable cells, was not.

Rogers and Dunn (1969) suggested that NNE may be related to the introduction of polyvinyl chloride catheters and feeding tubes and that a leaching out of plasticisers from the polyvinyl chloride produced a toxic disorder of vascular tone in the bowel wall. Hillman et al. (1975) reported substantial concentrations of plasticisers in segments of bowel wall in infants with NNE. However, only two of our infants had umbilical catheters inserted, one only after signs of the disease had developed, and Flynn et al. (1977), in their series, showed that the condition can occur in full-term healthy babies who have had no contact whatever with plasticisers.

Corkery et al. (1968) described three infants who had exchange transfusions for Rhesus incompatibility and who subsequently developed NNE. However, only one of our infants had exchange transfusion for Rhesus incompatibility, and Frantz et al. (1975), in a description of 54 cases with NNE, found that only three infants had had exchange transfusion before the onset of symptoms. They found that the frequency of NNE was not higher in patients receiving exchange transfusion than in those not receiving it.

Many authors agree that factors that cause hypoxia or ischaemia of the bowel wall are involved in the pathogenesis of the disease (Santulli et al., 1975; Leonidas and Hall, 1976; Bunton et al., 1977; Fairburn, 1977). However, the causes of the ischaemia or hypoxia are uncertain. Friedman et al. (1970) believe that exchange transfusion through an umbilical venous catheter situated in the portal system may produce retrograde microembolism or obstructive haemodynamic changes, resulting in haemorrhagic infarction of the gut. Rogers and Dunn (1969) state that plastic catheters introduced through the umbilical artery into the aorta cause thrombus formation which could compromise the blood flow to the bowel or cause embolisation. However, in an overwhelming majority of typical cases of NNE, no obstructive lesion such as thrombosis of the major blood vessels of the affected portion of the intestinal tract can be demonstrated (Joshi, 1977). It has been suggested that during periods of hypotension or stress in the perinatal period there may be a redistribution of blood away from the splanchnic circulation into more vital organs, resulting in mesenteric hypoperfusion. This, associated with hypoxia, results in secondary muscle spasm, further reducing the effective blood supply to the mucosa with resultant necrosis (Stevenson et al., 1971). Fairburn (1977) states that infants with diarrhoea (from whatever cause) associated with active peristalsis develop high intraluminal pressures in the colon, and these subject the bowel to an ischaemogenic influence. Two of our infants had clinical evidence of perinatal respiratory distress with a low Apgar score. However, Frantz et al. (1975), in a comparison of 54 infants with NNE and 98 controls, found that their data neither proved nor disproved the aetiological role of hypoxaemic intestinal damage.

The significance of pathogenic bacteria in NNE is difficult to ascertain (Hopkins et al., 1970). It is
thought that the ischaemia of the bowel is followed by bacterial invasion, proliferation, and gas production in the bowel wall (Lancet, 1977). Analysis of the gas in the cyst-like spaces has showed it to be composed largely of hydrogen and to be of microbial origin (Engel, 1975). Pedersen et al. (1976), in a description of a single case, showed that peroperative peritoneal swabs grew E. coli and Clostridium perfringens. Subtyping of six different isolates of the latter showed that three were type A (gas gangrene bacillus) and three were non-necrotising type A strains. He likens NNE to gas gangrene of the bowel, and Kosloske et al. (1978), in their series, reported that Cl. perfringens was invariably associated with the most severe and fatal cases. Klebsiellae have been recovered from the blood of some infants with NNE (Engel, 1975), and it does seem likely that an infectious component is operative in the condition.

If the origin of the gas-containing cyst-like spaces in the bowel wall is a result of proliferation of gas-forming organisms, particularly clostridia in the submucosa, and since the development of pneumatosis in NNE is fairly rapid, one would expect to find large colonies of organisms inside the cysts. This has not been our experience, and only occasional Gram-positive rods were seen inside some of the cyst-like spaces in the submucosa. Alternatively, it seems more likely that bacterially produced gas and toxins inside the lumen of the bowel may be forced through the necrotic mucosa into the submucosa. The observation that some of these cysts are partially lined by a single layer of flattened cells suggests that some of them are cystically dilated lymphatics and that gas is forced along them into the draining lymph nodes. We consider that Cl. perfringens and other organisms in the bowel wall are secondary invaders and are not involved in the primary pathogenesis of the disease. Cases 1 and 3 had the longest time intervals between the appearance of symptoms and surgical intervention, and the presence of multinucleated giant cells beneath the muscularis mucosa in case 3 and in the serosa of case 1 is difficult to explain. The presence of large numbers of eosinophils, often in clumps beneath the submucosa and in the serosa of all cases, may suggest an associated immune or allergic phenomenon. It is odd that all our cases occurred in the months December to March and that no instance of the disease occurred during the rest of the year.

To date no satisfactory explanation of the aetiology of NNE has been given. Various theories of pathogenesis have been suggested, none of which is above criticism, and we realise that our hypotheses can also be criticised.

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References


**Addendum**

A further infant with NNE presented to Kingston Hospital in January 1979. A full-term male baby weighing 3120 g was born by Caesarean section to a 24-year-old para 2 + 0. The Apgar score at 1 minute was 8. Signs of NNE were manifest at 50 hours after birth, and partial colectomy with end-to-end anastomosis was performed at 61 hours. Sections of the colon showed the appearances of NNE with mucosal necrosis and ulceration. Section of the terminal ileum showed no abnormality. Preoperative stool sent for anaerobic culture was negative. Gram stain of sections of colon showed moderate numbers of Gram-positive rods and cocci on the inner surface of the bowel and inside the necrotic mucosa. No organisms were seen inside the cyst-like spaces.

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