Summary

The occurrence and causation of nitrate-induced headache in industrial workers are reviewed, and three cases occurring in a pharmaceutical manufacturing plant are described. The mode of production of this troublesome syndrome and the ease with which it may be prevented are outlined. The relevant literature is reviewed in the context of the account.

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Medical Memoranda

Pneumatosis Cystoides Intestinalis

Until recently the condition of pneumatosis cystoides intestinalis had rarely been described as involving the large bowel. In only 9 out of 213 cases reviewed by Koss (1952) was the colon the sole site of the disease; the majority involved the small intestine and its peritoneal attachments.

When the large bowel has been implicated, the condition has usually been recognized as the result of symptoms either of dysfunction or of mechanical obstruction of the bowel, directly attributable to the presence of the cysts. This contrasts to the so-called "secondary pneumatosis" of the small intestine related to other pathological processes such as peptic ulceration or neoplasm, which are the prime cause of symptoms. In the large bowel, although previous sigmoidoscopy or minor operative procedure such as polypectomy has been the implied causative factor in the production of the cysts (Marshak *et al.*, 1956), the condition may develop spontaneously. To such cases the term "primary pneumatosis" may accurately be given, and an increasing number of such examples have appeared in recent years in the literature.

The presence of gas cysts affecting the sigmoid colon, and associated with recurrent volvulus of the affected loop, was reported by Jones (1948). Resection was performed in this patient. Witkowski *et al.* (1955) described a case where symptoms of large-bowel obstruction led to the diagnosis, again with resection of the affected portion of bowel as the outcome. A disturbing feature was the later appearance of further cysts in the remain-

ing colon, with no evidence of a tendency to spontaneous remission. Griffiths (1955) reported a case in which pain in the left iliac fossa and passage of mucus and blood per rectum were the presenting symptoms. Diagnosis was made on radiological and sigmoidoscopic findings, and later subacute obstructive symptoms supervened, necessitating resection of the affected bowel. Shoemith and Crone (1959) have treated two further patients in whom the left colon was involved; in one the cystic changes extended into the rectum.

We record below yet another example of severe pneumatosis cystoides intestinalis affecting the left colon and presenting as a volvulus of the involved loop.

CASE REPORT

The patient, a man of 38 and a known severe epileptic, was admitted to hospital on January 18, 1959. He gave a history of severe lower abdominal pain of sudden onset, occurring while he was in bed three hours before admission. He had vomited once, immediately after the onset of the pain, and stated that for the previous three days his motions had been "rather loose."

The past history was difficult to assess as he was of low intellect, being cared for at home by his sister. He had never worked, and epileptiform attacks were frequent despite prolonged and heavy drug treatment. There was no history of dyspepsia or of previous abdominal pain. His sister volunteered the information that he tended to be constipated and had been known to introduce foreign bodies into his rectum.

On admission he was found to be a poor witness, in some pain, but this was apparently much less severe than at the onset. The abdomen was distended, but without rigidity or localized tenderness. Rectal examination showed no evidence of any foreign body or local trauma, and the rectum was empty. His general condition was good, with no evidence of shock. Plain x-ray films of the abdomen in the erect and supine positions demonstrated considerable distension of the large bowel, without the presence of fluid levels. No faecal result was obtained from two enemas.

After admission his pain subsided and it was decided to pursue a conservative regime. There was no further vomiting, and he became less distended, with passage of flatus and some fluid faeces per rectum. Pain recurred, however, and on January 23 a small amount of barium was run into the rectum. This demonstrated an apparent complete obstruction at the recto-sigmoid junction. The barium was retrieved, and sigmoidoscopy demonstrated an impassable obstruction at 20 cm. from the anal margin. It was thought that he had either a recurring volvulus at the recto-sigmoid junction or an impacted foreign body. Laparotomy was performed.

At operation a volvulus of the sigmoid loop through 180 degrees was found to have occurred. The loop of bowel involved was greatly enlarged, but it untwisted readily and was perfectly viable. On examination the affected loop was found to be the site of multiple gas cysts, encroaching on the lumen and projecting on the serosal surface. The rectum and rest of the bowel were quite normal in appearance, there being no evidence of any coincidental lesion in the stomach or intestine. Attempted deflation resulted in very little diminution in the size of the bowel, and the affected portion was resected by the Mikulicz procedure.

HISTOPATHOLOGY

The resected bowel consisted of sigmoid colon, measuring 40 cm. in length, and 13 by 9 cm. in cross-section at its largest part, after fixation. The great increase in diameter was due to the large number of gas-filled cysts situated in the bowel wall, giving the specimen a spongy consistency on palpation.

The gas was completely confined to the cysts, and could not be forced from one cyst to the next or into the lumen of the colon. The cysts could be made to rupture on moderate pressure.

The cut surface (Fig. 1) showed solitary cysts up to 5 cm. in diameter, but most were divided into smaller cavities by thin white septa. The largest multilocular cyst was 8 cm. in diameter, and the smallest 0.4 cm. All the cysts had a smooth, white glistening internal surface, and were empty of any solid or liquid content. The mucous membrane of the colon appeared normal and the lumen was not appreciably narrowed.

There was no macroscopic evidence of neoplasm or inflammation, other than some congestion of the external surface.

Histological sections (Fig. 2) demonstrated that the cysts occupied the submucous layer, between the muscularis mucosae and the inner circular muscle layer of the colon. The cysts were subdivided by thin fibrous septa, lined for the most part by a thin single layer of flattened cells, resembling endothelial cells. These cells contained elongated nuclei and eosinophilic cytoplasm. In a few places the endothelium appeared incomplete, and in other places assumed cuboidal form.

Moderate numbers of multinucleate foreign-body giant cells were present in the lining of the cysts. These ranged from elongated cells with two or three nuclei to large giant cells with thirty or more nuclei. All gradations were seen, from the single flat endothelial cell to the large giant cell. These giant cells were more numerous towards the mucosal

FIG. 1.—Resected specimen of sigmoid colon.

FIG. 2.—Low-power photomicrograph, showing gas cysts in the submucous layer. There is evidence of congestion of the serous coat.

side of the specimen, and some appeared to be partially detached from the wall of the cyst.

The serous coat showed oedema, early acute inflammatory change with congestion, and diapedesis of polymorphonuclear cells. Dense focal accumulations of acute inflammatory cells were present. The mucous membrane showed oedema, with early and superficial ulceration of the epithelium in places. These latter changes were probably related to the volvulus. The patient's progress after operation was slow, principally owing to increasing epileptic attacks and deterioration in his mental condition. The double-barrelled colostomy was closed by intraperitoneal technique on February 19, and opportunity was taken for re-exploration of the abdomen on that occasion. No further cysts were seen in remaining bowel.

Further deterioration in his epileptiform state necessitated his remaining in hospital until April 28. At that time his bowels were open regularly and he had no abdominal symptoms.

COMMENT

In considering the pathogenesis of pneumatosis cystoides intestinalis several theories have been advanced. Some are substantiated by factual evidence, others are purely conjectural. The condition has been described in infants, but must be regarded as an acquired rather than a congenital disorder. In a series of infants reviewed by Paris (1955) the gas cysts were invariably associated with an acute enteritis.

It is generally accepted that the cysts represent distended lymphatic channels, both on the evidence of the position of the cysts and on their histological appearance. However, no truly satisfactory reason for the gaseous distension has been advanced and proved without doubt.

Of the many theories, the mechanical one impresses most. Here it is postulated that a breach in the intestinal mucosa allows the abnormal entrance of gases, which permeate into near-by lymphatics. Increased intraluminal pressure, admittedly of doubtful origin, serves to increase the gaseous influx, with consequent distension of the resultant cysts by a purely mechanical process. Such breaches in the mucosa occur in the presence of intestinal ulceration or neoplasm, in enteritis, and after such procedures as sigmoidoscopy and polypectomy. If this is so, it is surprising that the condition has not been recognized more often, though this may be due to the rapid disappearance of gas cysts by a process of gaseous absorption or rupture. Such a theory would explain the not infrequent occurrence of spontaneous pneumoperitoneum recognized as an incidental finding while radiological studies of the abdomen are being made.

A possible explanation is that an alteration occurs in the permeability of the mucosa. This may result from the presence of near-by disease, enteritis, or a nutritional deficiency. In support of the latter, a condition of pneumatosis of the intestines of swine has been produced experimentally by feeding them solely on a diet of polished rice.

It may be reasonable to combine the mechanical and disordered permeability theories. An increased intraluminal pressure, occurring for example during defaecation, vomiting, or at sigmoidoscopy, may well increase the tendency to gaseous diffusion in a mucosa already of suspect permeability.

Whether or not cysts arise secondary to an episode of intestinal obstruction is a matter for conjecture. Sauser-Hall (1940) suggested that this might be so, but the reverse is generally accepted. Obstruction may occur

owing to the very bulk of the cysts, or an intussusception or volvulus be precipitated by their presence.

X-ray Studies.—Characteristic radiological patterns have been described, and preoperative diagnosis has on occasion been made correctly by virtue of the x-ray appearance. Certainly x-ray studies offer the most useful diagnostic aid (Marshak *et al.*, 1956). Films of the abdomen in the erect position may demonstrate grape-like clusters of air shadows, the walls of the bowel being delineated by a double contour line (Paris, 1955). In colonic involvement, and in the absence of complete obstruction as occurred in our case, x-ray films after a barium enema may reveal the gas cysts as discrete lucent areas, indenting the regular contour of the bowel as a series of filling defects of varying sizes. Differentiation between gas cysts and diffuse polyposis may be difficult, however. The occasional occurrence of pneumoperitoneum has already been commented upon.

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Carcinoma of the Colon in a Child

Hoerner (1958) was able to collect 73 cases of carcinoma of the colon and 189 of carcinoma of the rectum occurring in subjects under 20 years of age and published between 1865 and 1958. Since then a case of carcinoma of the colon has been reported by Kern and White (1958) and three cases were added by Salem and Postlethwait (1960). Carcinoma of the colon may also occur in children in association with ulcerative colitis (Wilcox and Beattie, 1956). Compared with other neoplasms occurring in children, carcinoma of the colon is rare, there being no cases of this disease in a series of 965 children under 15 years with tumours quoted by Saner (1946).

CASE REPORT

A girl aged 13 years and 10 months, with no family history of intestinal disease, was first seen on November 23, 1959. In late 1957 she had started to complain of non-specific abdominal pain which recurred at intervals of about two to three months and lasted for a day or two at a time. In March, 1959, she began to have shooting pains in both groins which became worse, occurring about 10 times in each 24 hours by the time she was seen. Her mother thought she had lost weight. Her bowels had been normal; her appetite was poor, but she had had no nausea or vomiting. Menstruation had not begun, and her mother said that her two sisters had had similar troubles at puberty. On examination she weighed 4 st. 10½ lb. (30.3 kg.). No abnormal physical signs were found, but it was noted that no secondary sex characters had appeared. An E.S.R. was 12 mm. in one hour (Westergren).

During the next month she vomited three times, and the pain became localized to the umbilical region, slightly more severe, and more colicky in nature. Her bowels remained normal.

On December 24 she was admitted to hospital with increasingly severe colic. She had passed four loose motions on the day of admission. No definitely abnormal signs were found and her symptoms rapidly settled over the next two days. She had lost 2 lb. (0.9 kg.) in weight since her first attendance. An E.S.R. was 7 mm. in one hour (Westergren); Hb, 97%; W.B.C., 7,200/c.mm. The stool contained no pathogens or blood.

Her progress was followed as an out-patient during January, 1960, her weight continuing to fall. Her pain was less severe and she said she had dysuria. Guarding in the left hypochondrium was found. An intravenous pyelogram and urine examination were negative. At the beginning of February she complained of diarrhoea twice daily and said that her motions were occasionally streaked with blood. Her colic was again becoming worse and her abdomen had become slightly distended. She was readmitted on February 8.

Physical Findings.—She was a thin, wasted child weighing 4 st. 0 lb. 3 oz. (25.5 kg.), with follicular hyperkeratosis and no signs of puberty. The pulse rate was 80, and blood-pressure 110/70. She was tender in the left iliac fossa, but no mass was felt. Her abdomen was slightly distended with gas.

Investigations.—Hb, 93% (Haldane); W.B.C., 4,500/c.mm.; E.S.R., 11 mm./hour. Stool: occult blood present, no tubercle bacilli, fat excretion 2 g. a day. A sigmoidoscopy was reported on as being normal to 15 cm. A barium-enema examination (Fig. 1) showed a narrowed segment in the mid-descending colon extending almost to the splenic flexure. A diagnosis of Crohn's disease was suggested by the radiologist. A barium meal disclosed no abnormalities but caused an episode of acute intestinal obstruction lasting 24 hours.

Course and Treatment.—She contracted chicken-pox on February 30. On March 31 a laparotomy was performed

FIG. 1.—Barium enema showed a narrowed segment in the mid-descending colon extending almost to the splenic flexure.