

# Breath hydrogen in pneumatosis cystoides intestinalis

J. GILLON<sup>1</sup>, K. TADESSE, R. F. A. LOGAN, S. HOLT, AND W. SIRCUS

From the Gastrointestinal Unit and Wolfson Laboratory, Western General Hospital, Edinburgh, and the Department of Therapeutics, University of Edinburgh, Royal Infirmary, Edinburgh

**SUMMARY** Pneumatosis cystoides intestinalis (PCI) is an uncommon condition of unknown aetiology. Bacterial gas production may be an important aetiological factor, but experimental evidence in humans has been lacking. We have studied breath hydrogen excretion as an index of bacterial gas production in 12 patients with PCI and have shown that four out of five with demonstrable cysts produced unusually high levels of hydrogen while fasting. This abnormality has not been previously reported. One patient showed resolution of PCI after antibiotic treatment. These findings confirm the importance of bacterial gas production in the pathogenesis of PCI.

There has been much speculation about the aetiology of pneumatosis cystoides intestinalis (PCI), an uncommon condition characterised by the presence of gas-filled cysts within the walls and mesentery of the intestine. The most widely accepted theories have proposed a mechanical origin for the cysts (Koss 1952; Keyting *et al.*, 1961), but mechanical theories alone fail to account for the finding that hydrogen, a gas never produced by mammalian cells, may comprise up to 50% of the gas content of the cysts (Forgacs *et al.*, 1973).

Measurement of breath hydrogen is now an established method of studying bacterial activity in the intestine (Hepner, 1974) and we have therefore studied breath hydrogen excretion in our patients with PCI.

<sup>1</sup>Address for correspondence: Dr J. Gillon, Gastrointestinal Unit, Western General Hospital, Edinburgh EH4 2XU.

Received for publication 16 May 1979

## Methods

### PATIENTS

Twelve patients with previous clinical and radiological evidence of pneumatosis were studied. Eleven had cysts confined to the colon, while one had extensive small intestinal involvement. Details of the patients, including associated diseases, are given in the Table.

Five of the 12 patients had demonstrable cysts at the time of the study. Seven patients had previously undergone high-flow oxygen treatment, and of these four remained in remission. One patient had sigmoid volvulus in association with pneumatosis coli requiring surgical resection, and one patient had achieved spontaneous remission. In one case resolution of primary pneumatosis coli had been observed after a two-weeks' course of ampicillin, given because of an intercurrent urinary tract infection (Holt *et al.*, 1978).

Table Details of 12 patients with PCI

Patient	Sex	Age (yr)	Other diseases	Extent of pneumatosis	O <sub>2</sub> treatment
1. G. S.	F	72	Diverticular disease	Small intestine	—
2. J. S.	M	54	DU, chronic bronchitis	Descending colon	+
3. W. P.	F	55	Osteoarthritis lumbar spine	L half of colon	+
4. R. G.	F	69	—	Total colon	+
5. I. S.	M	68	Diabetes mellitus	Sigmoid colon	+
6. K. P.	F	67	—	L half of colon	—
7. A. B.	F	38	—	Sigmoid colon	+
8. T. G.	M	61	—	Sigmoid colon	—
9. J. A.	M	70	—	L half of colon	—
10. A. M.	F	59	Diverticular disease + osteomalacia	L half of colon	+
11. J. M.	M	63	CVA, chronic bronchitis	L half of colon	+
12. E. S.	F	61	CVA	L half of colon	—

DU: Duodenal ulcer. CVA: Cerebrovascular accident.

## PROCEDURE

Patients were studied after an overnight fast. End-expiratory alveolar air samples were collected in plastic syringes and the hydrogen content measured by gas chromatography (Pye Series 104). Details of the method have been published previously (Tadesse and Eastwood, 1978). Several fasting samples were taken and the patient was then given 50 g glucose orally. Thereafter breath hydrogen excretion was measured at 15-minute intervals for 2½ hours.

Plain abdominal radiographs were taken on the day of the test.

## Results

Fasting breath hydrogen was found to be greater than 1.0  $\mu\text{mol/l}$  (normal range 0-1.0  $\mu\text{mol/l}$ ) in six of the 12 patients (Fig. 1). Four of these patients had demonstrable cysts, while only one of the six patients with levels below 1.0  $\mu\text{mol/l}$  had evidence of pneumatosis on the day of the study. The results of

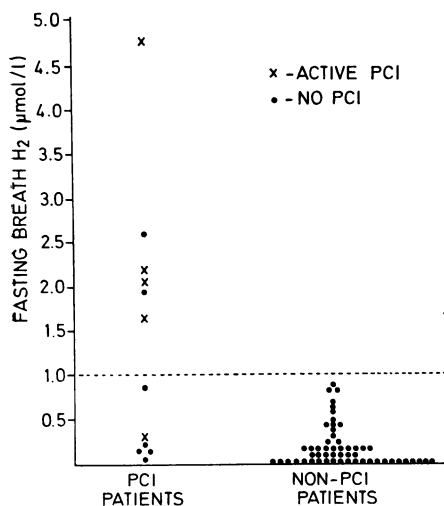


Fig. 1 Fasting breath hydrogen levels in 12 patients with PCI and 54 patients without pneumatosis.

fasting breath hydrogen in all patients so far having undergone investigation for other reasons are also shown in Fig. 1. These include inflammatory bowel disease, post-vagotomy diarrhoea, and irritable bowel syndrome. It will be seen that all of these patients, with diverse gastrointestinal disease, excreted less than 1.0  $\mu\text{mol/l}$  in the fasting state. Pneumatosis cystoides intestinalis is therefore the only condition that we have studied in which a raised fasting breath hydrogen has been demonstrated.

The response to orally ingested glucose is shown

in Fig. 2. Four patients show a substantial increase in breath hydrogen at a variable interval after glucose (Fig. 3), indicating that this absorbable

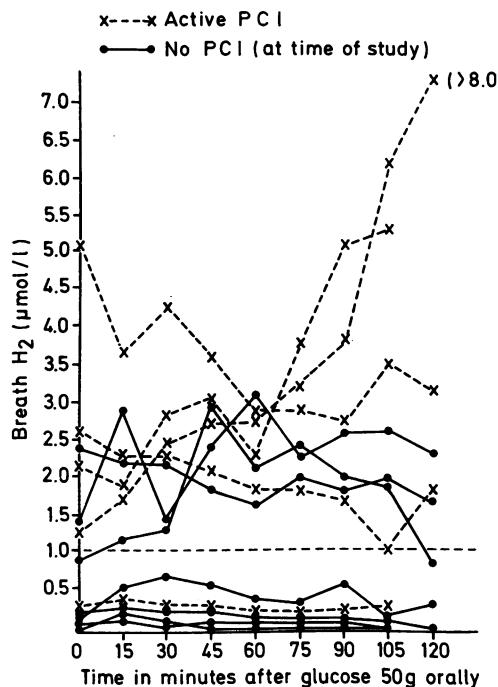


Fig. 2 Breath hydrogen response to glucose 50g orally in 12 patients with PCI.

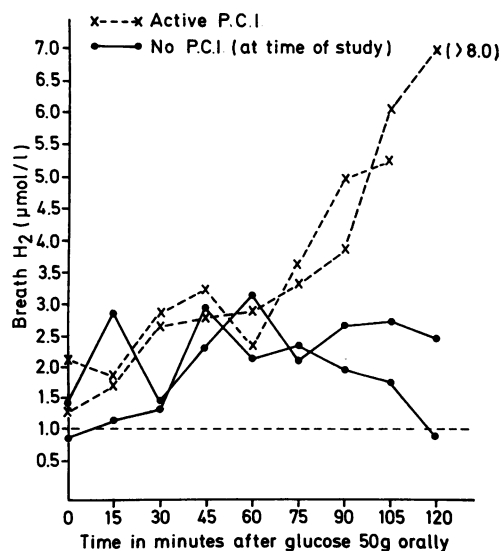


Fig. 3 Breath hydrogen response to glucose 50g orally in four patients with PCI.

carbohydrate had made contact with gas-forming organisms. Pneumatosis had been confined to the colon in three of these patients.

To examine the possibility that this response to ingested glucose might arise from absorbed glucose reaching the bacteria *via* the bloodstream, we measured the breath hydrogen response to intravenous glucose (25 g as a bolus injection) in five of our patients. No rise in hydrogen excretion after intravenous glucose was observed in spite of substantial rises in plasma glucose.

One patient (GS) with extensive small intestinal pneumocysts had a raised fasting breath hydrogen and a striking response to ingested glucose (Fig. 4). After three weeks' treatment with tetracycline 250 mg four times daily she was asymptomatic and a plain abdominal radiograph showed complete resolution of pneumatosis. Further studies revealed that, although the pattern of response to glucose remained unchanged, the fasting breath hydrogen had been reduced to normal levels.

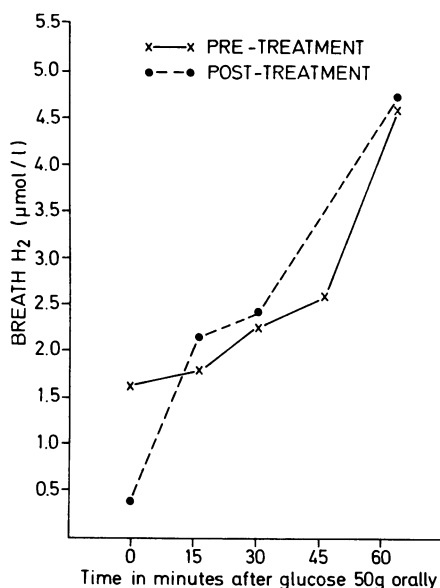


Fig. 4 Breath hydrogen response to oral glucose in patient G.S., before and after tetracycline 250 mg *q.i.d.* for three weeks. Note return of fasting value to normal.

## Discussion

Previous research into the aetiology of pneumatosis cystoides intestinalis has tended to concentrate on the initiating mechanism which allows gas to collect in the submucosal and subserosal tissues. Pneumocysts are known to occur in association with various conditions, particularly peptic ulceration, pyloric

stenosis, intestinal obstruction, and chronic obstructive airways disease (Koss 1952; Doub and Shea 1960; Keyting *et al.*, 1961). The association with peptic ulceration led Koss (1952) to believe that gas from the lumen could enter the submucosa by way of a mucosal breach, while Keyting and colleagues, noting the reported high incidence of chronic bronchitis in pneumatosis patients, proposed that air escaping from a ruptured alveolus could track along the adventitia of the great vessels to the abdomen, and hence to the mesentery and bowel wall. This theory received support from animal experiments. Pneumatosis has also been described in association with colonoscopy (Wertkin *et al.*, 1976), anorectal surgery (Marino, 1958), and jejunioleal by-pass (Martyak and Curtis, 1976) and it is clear that gas may enter the bowel wall in various circumstances.

Pneumocysts may, however, persist for long periods of time and the mechanical theories fail to explain how the cysts are maintained once formed. Extraintestinal gas pockets—for example, surgical emphysema or pneumoperitoneum—are normally reabsorbed quite rapidly, as the partial pressures of oxygen, water, and carbon dioxide rapidly equilibrate with those of venous blood, leaving a partial pressure gradient for nitrogen which leads to reabsorption (the total partial pressure within the cysts necessarily remaining at or above atmospheric). In the case of pneumocysts, reabsorption would be prevented if the partial pressure of nitrogen were reduced to that of venous blood. This could occur only if gases other than those found in venous blood were to exert a partial pressure of at least 55 mm Hg (Forgacs *et al.*, 1973). The finding of hydrogen and other gases in the cysts (Forgacs *et al.*, 1973) indicates that these gases, which are not produced by mammalian cell metabolism, may fulfil this role, and the ready diffusibility of hydrogen into the bloodstream means that a constant supply would be necessary. Our finding that four of the five patients with active pneumatosis excrete large quantities of hydrogen, even while fasting, provides the first experimental evidence in humans that constant hydrogen production by bacteria may be the mechanism whereby the cysts persist.

Additional support for this was obtained by treating one patient with extensive small bowel pneumatosis with antibiotics. Complete symptomatic and radiological remission was obtained and, although for reasons unknown the breath hydrogen response to glucose remained positive, the previous high fasting level of breath hydrogen was restored to normal. The constant production of hydrogen might therefore have been interrupted, allowing reabsorption to occur.

A surprising finding was the positive breath hydrogen response to oral glucose in four patients. Since glucose is usually absorbed completely in the jejunum (Borgstrom *et al.*, 1957) we considered the possibility that glucose was reaching the bacteria by way of the bloodstream, a theory which would also explain the origin of the substrate for hydrogen production in the fasting state. However, our data on hydrogen excretion after intravenous glucose fail to support this hypothesis. The variable time course of the response to oral glucose suggests that the hydrogen production may result from relatively small amounts of unabsorbed glucose reaching the diseased area.

Pneumatosis has been produced in germ-free rats by the injection of *Clostridia* species into the wall of the bowel or peritoneal cavity (Yale and Balish, 1976). However, isolation of the organisms from the resulting lesion often proved impossible, demonstrating the difficulty in culturing fastidious anaerobes. The failure to demonstrate bacteria within human cysts using conventional techniques does not necessarily exclude their presence and a different approach to the detection of organisms—for example, using electron micrography—might prove rewarding.

Evidence for a bacterial factor in the aetiology of PCI has previously been obtained only from animal experiments. Our results show that bacterial gas production is an important feature of pneumatosis cystoides intestinalis in humans. Although gas, and possibly bacteria, can enter the intestinal wall in various circumstances, it seems likely that the cysts persist only in the presence of abnormal bacterial gas production.

We would like to thank the World Health Organisation for assistance with a Fellowship (KT) and Dr R. C. Heading for allowing us to study patients under his care. We also acknowledge the contribution of Mr A. N. Smith to the initiation of this research.

## References

- Doub, H. P., and Shea, J. J. (1960). Pneumatosis cystoides intestinalis. *Journal of the American Medical Association*, **172**, 1238-1242.
- Borgstrom, B., Dahlqvist, A., Lundh, G., and Sjovall, J. (1957). Studies of intestinal digestion and absorption in the human. *Journal of Clinical Investigation*, **36**, 2, 1521-1536.
- Forgacs, P., Wright, P. H., and Wyatt, A. P. (1973). Treatment of intestinal gas cysts by oxygen breathing. *Lancet*, **1**, 579-582.
- Hepner, G. W. (1974). Breath analysis: gastroenterological applications. *Gastroenterology*, **67**, 1250-1256.
- Holt, S., Stewart, I. C., Heading, R. C., and MacPherson, A.I.S. (1978). Resolution of primary pneumatosis coli. *Journal of the Royal College of Surgeons of Edinburgh*, **23**, 297-300.
- Keyting, W. S., McCarver, R. R., Kovarik, J. L., and Daywitt, A. L. (1961). Pneumatosis intestinalis: a new concept. *Radiology*, **76**, 733-741.
- Koss, L. G. (1952). Abdominal gas cysts (pneumatosis cystoides intestinorum hominis): an analysis with a report of a case and a critical review of the literature. *Archives of Pathology*, **53**, 523-549.
- Marino, A. W. M., Jr. (1958). Pneumatosis intestinalis complicating anorectal surgery. *Diseases of the Colon and of the Rectum*, **1**, 167-171.
- Martyak, S. N., and Curtis, L. E. (1976). Pneumatosis intestinalis: a complication of jejunoileal by-pass. *Journal of the American Medical Association*, **235**, 1038-1039.
- Tadesse, K., and Eastwood, M. A. (1978). Metabolism of dietary fibre components in man assessed by breath hydrogen and methane. *British Journal of Nutrition*, **40**, 393-396.
- Wertkin, M. G., Wetchler, B. B., Wayne, J. D., and Brown, L. K. (1976). Pneumatosis coli associated with sigmoid volvulus and colonoscopy. *American Journal of Gastroenterology*, **65**, 209-214.
- Yale, C. E., and Balish, E. (1976). Pneumatosis cystoides intestinalis. *Diseases of the Colon and Rectum*, **19**, 107-111.