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# Factors Affecting Methane Production in Humans

## Gastrointestinal Diseases and Alterations of Colonic Flora

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*Breath methane was studied in 394 subjects. Among 152 controls, 50.0% produced methane—42.1% of males and 57.9% of females. One hundred sixteen patients with gastrointestinal diseases were studied. Among 32 with Crohn's disease, only 2 (6.1%) produced methane, as well as 16 of 51 ulcerative colitis patients (31.4%) and 11 of 32 patients with the irritable bowel syndrome (34.4%). Breath methane is thus unusual in Crohn's disease. After bowel cleansing for colonoscopy or surgery, 15 of 18 methane producers became nonproducers, whereas after antibiotic treatment, 24 of 30 producers sustained their methane-producing status. After gentamycin and cephazolin therapy, methane production was abolished in three of eight patients. Slight spontaneous variations in methane production were also noticed with two of 23 control subjects, becoming nonproducers on restudy after 10–25 months. Thus gastrointestinal diseases, bowel cleansing and, to a much lesser degree, antibiotic therapy, affect methane production.*

The phenomenon of methane production in humans has attracted increasing interest during the last decade (1–4). However, the factors causing methane formation or nonformation are not known. The production of methane by the colonic flora begins at the age of 3 years. The incidence of methane production is influenced by sex and ethnic origin (2, 5, 6). Other factors affecting methane production are still under investigation. Bond et al (5) suggested the general importance of environmental factors. Pentoses were shown to increase methane production *in vivo* (7), whereas the effect of lactulose is controversial (2, 5, 8). Colon cancer has been claimed by Haines et al (1) and Pique et al (9) to increase methane production, but other groups could not reproduce these data (4, 10). Vascular ischemia (11), cystic fibrosis (12), as well as some gastrointestinal diseases were shown to affect methane production (4).

In this study we present our results in patients with gastrointestinal diseases and evaluate the influence of antibiotic treatment and preparation for colonoscopy and colonic surgery on methane formation.

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## MATERIALS AND METHODS

**Subjects.** Group 1, the control group, consisted of 152 healthy staff members of the hospital (76 males and 76 females) aged 18–70 (mean 39.8 years). Twenty-three methane producers from this group were restudied after 10–25 months.

Group 2 consisted of 116 patients attending the gastrointestinal clinic (56 males and 60 females) aged 16–84 (mean 47.0) years. In this group were 51 patients with ulcerative colitis, 33 with Crohn's disease (nine had disease of the small bowel, 14 ileocecal, and 10 colonic disease), and 32 with the irritable bowel syndrome. The diagnoses were based on standard x-ray, endoscopic, and clinical parameters. Absorption tests were performed when needed.

In group 3 were 86 patients treated with antibiotics. They were mostly patients hospitalized in the medical wards for urinary tract infections, pneumonia, obstructive lung disease, and other disease states requiring antibiotic therapy.

Group 4 was made up of 26 patients undergoing colonoscopy and 14 undergoing colonic surgery for carcinoma of the large bowel. Some colonoscopy subjects were patients with gastrointestinal diseases included in group 2.

Subjects from groups 1, 2, and 3 were studied during the day, in the nonfasting state. Subjects from group 3 were studied several hours after admission (before or at the beginning of antibiotic treatment) as well as towards the end of treatment (mostly after 3–5 days). The patients undergoing coloscopy or surgery were studied several days before and, if they were found to be methane producers, they were restudied at the day of the procedure. The preoperative patients were restudied in the fasting state on the day of operation. In all subjects smoking was avoided for at least 30 min before air sampling. Samples of ambient air were always taken at the locations where subjects were studied.

Preparation of patients for colonoscopy and colon surgery was as previously described (13).

**Collection of Expired Air and Methane Analysis.** Expired air was completely collected for 2–4 min, using a system previously described (6). The subjects breathed through a mouthpiece mounted on an AMBU E-valve into a 40-liter meteorologic balloon, from which a 20-ml air sample was drawn. Methane air concentration was analyzed using a GCD gas chromatograph (Pye Unicam) equipped with a Porapak Q column and a flame ionization detector (6). A subject was considered a methane producer if his breath methane concentration was at least 1 ppm above ambient air (5).

## RESULTS

**Group 1—Controls.** Seventy-six of 152 controls were methane producers (50.0%). Their breath methane concentration was 10.2 ± 9.1 ppm (mean ± SD). When 23 methane producing controls were restudied after 10–25 months, two were found to be nonproducers. The previous breath methane concentrations of these two subjects were 7.7 and 8.6 ppm. The mean values are shown in Figure 1.

**Group 2—Patients with Gastrointestinal Diseases.** Among the 51 patients with ulcerative colitis, 16 were methane producers (31.4%). Among 33 patients with Crohn's disease, only two were methane producers (6.1%). Among 32 patients with the irritable bowel syndrome, 11 were methane producers (34.4%). In 16 of these patients with constipation, five (31.2%) produced methane. Among six of these patients with diarrhea one produced methane (16.6%).

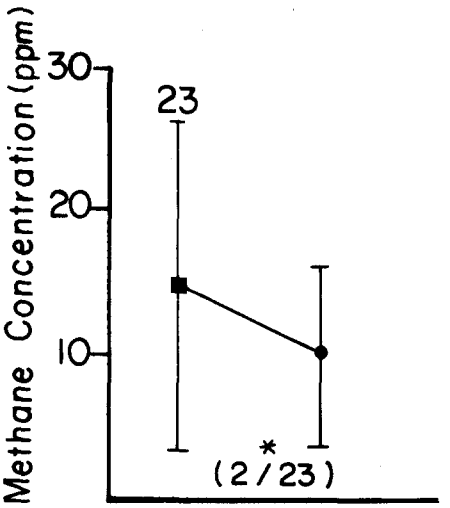


**Fig. 1.** Methane concentration (mean ± SD) in methane-producing controls restudied after 10–25 months. Squares, initial sample; circles, second sample. Numbers, number of subjects studied. *Proportion of methane-producing subjects who were found to be nonproducers on restudy.

**Group 3**—Among 86 patients beginning antibiotic therapy, 56 were methane producers (65.1%). In 30 methane-producing patients, a second breath sample was obtained during antibiotic therapy, usually after 3–5 days. The mean data for various antibiotics and combinations of antibiotics are given in Figure 2. Six of the 30 patients became methane nonproducers during antibiotic therapy. In two, the change was minimal (from 1.5 and 2.2 ppm to 0.4 and 0.7, respectively). In three it was substantial (from 7.1, 6.0, and 3.1 ppm to 0.3, 0.2, and 0.2 ppm, respectively) and in one, very marked (from 36.5 to 0.9 ppm).

In the remaining 24 patients, methane concentration increased in 17 and decreased in 7. The mean methane concentration did not change significantly. Looking at various antibiotics, mean methane concentration rose insignificantly in four groups and decreased insignificantly in patients receiving gentamycin and cefazolin as well as in patients receiving penicillin. In the group receiving gentamycin and cefazolin, three of eight patients became nonproducers.

Among 26 patients scheduled for colonoscopy, 14 were found to be methane producers and were restudied following bowel preparation just prior to the procedure. Only two were still producing methane with concentrations of 2.8 and 2.1 ppm, in comparison to initial concentrations of 4.5 and 6.2 ppm, respectively.

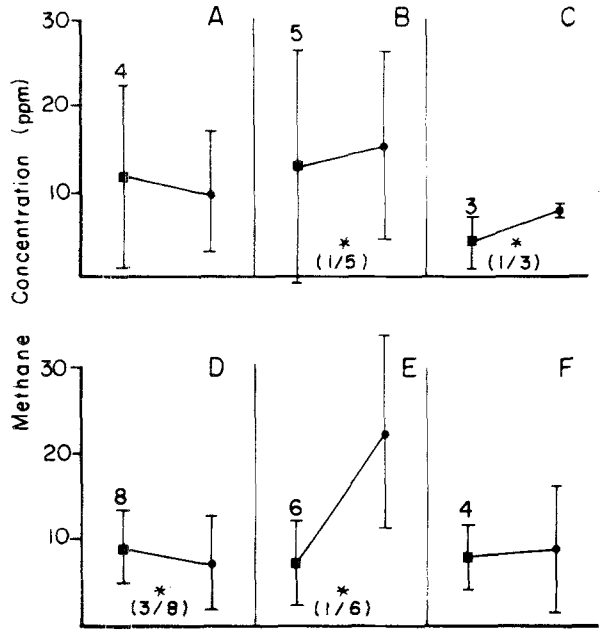


Fig. 2. Methane concentration (mean ± SD) in methane-producing subjects before and during various antibiotic treatments. Squares, before treatment; circles, during treatment. Numbers, number of subjects studied. *Proportion of methane-producing subjects who were found to be nonproducers during therapy. A, penicillin; B, ampicillin; C, ampicillin + gentamycin; D, gentamycin + cefazolin; E, cefazolin; F, trimethoprim + sulfomethoxazole.

Among 14 patients having colon cancer, six were found to be methane producers. Two were not operated. Of four who were restudied following bowel preparation on the day of operation, three were found to be nonproducers. Methane concentration of the fourth was 1.4 ppm compared to the initial concentration of 18.5 ppm. Results for all study groups are given in Table 1.

## DISCUSSION

Among the patients with gastrointestinal diseases the most striking difference in methane production was found in patients with Crohn's disease (CD). Only two of 33 patients (6.1%) produced methane, compared to 50.0% among controls and more than 30% in patients with ulcerative colitis (UC) and the irritable bowel syndrome (IBS). This finding has been noted by others: Bjorneklett et al. (14) found no methane producer among 28 patients with CD and McKay et al (4) reported five methane producers out of 40 patients (12.5%). The patients studied by Bjorneklett had disease of the small bowel only, whereas ours as well as McKay's patients had mostly ileocolonic or colonic disease.

Considering the difficulty, in some cases, of differentiating between CD and UC, methane production in a patient would weigh against CD. Thus, methane breath analysis may have some diagnostic value in CD. Of our two patients with CD who produced methane, one with colonic disease was in complete remission for six years and was receiving sulfasalazine. The other had active disease affecting mainly the small bowel.

The basic causes of methane production or nonproduction are still not understood, therefore the mechanism of methane nonproduction in CD is unknown. It cannot be attributed to diarrhea as this exists also in UC and IBS. The methane-producing microorganisms (methanogens) belong to the Archaebacteria, a kingdom distinctly different from the Eubacteria, the true bacteria, which inhabit the human colon. They present a metabolically unique type of strict anaerobes, and may be susceptible to changes in redox potential.

Patients with UC produced methane less frequently than controls. The difference in our series was confined to women, of whom only 24% produced methane compared to 57.9% in the controls ($P < 0.05$). McKay et al (4) found that only 15% of 40 patients with UC produced methane. It is, in our opinion, too early to conclude whether patients with UC produce methane significantly less frequently than controls.

Patients with IBS, half of them constipated, produced methane in a proportion similar to those with UC. Since constipation does not seem to affect methane production and since in both CD and UC diarrhea is present, more data are needed on the effect of diarrhea *per se* as a potential factor in methane production. McKay et al (4) did not find a marked reduction in the proportion of methane producers among 40 patients with IBS as well as in 94 patients with nonspecific diarrhea.

Patients with UC and IBS had higher methane concentrations in comparison to controls. The differences were not statistically significant.

The ability to produce methane is supposed to be acquired at age 3, reach adult incidence at age 10 and persist throughout life (5). We have shown that this ability develops much more gradually from 6.4% methane producers at age 3 to 18.2% at 11 years (6).

A few studies have addressed the question of whether methane production is a constant phenom-

TABLE 1. METHANE PRODUCTION IN STUDY GROUPS

| Group | All | | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|---|---|
| | *No.* | *% Producers* | *Methane conc.** | *No.* | *% Producers* | *Methane conc.** | *No.* | *% Producers* | *Methane conc.** |
| 1. Control | 152 | 50.0 | 10.2 ± 9.1 | 76 | 42.1 | 8.8 ± 9.5 | 76 | 57.9 | 11.2 ± 8.8 |
| 2. GI diseases | | | | | | | | | |
| UC | 51 | 31.4 | 19.7 ± 19.3 | 26 | 38.5 | 19.2 ± 13.1 | 25 | 24.0 | 21.0 ± 28.1 |
| CD | 33 | 6.1 | 10.6 ± 2.7 | 18 | 5.6 | 8.7 | 15 | 6.7 | 12.5 |
| IBS | 32 | 34.4 | 20.1 ± 15.8 | 12 | 25.0 | 15.0 ± 11.6 | 20 | 40.0 | 22.0 ± 17.4 |
| 3. Antibiotics | | | | | | | | | |
| Pretreatment | 86 | 65.1 | 8.9 ± 7.1 | 49 | 67.3 | 9.2 ± 7.7 | 37 | 62.2 | 8.6 ± 6.3 |
| On therapy | 30 | 80.0 | 12.7 ± 9.3 | 18 | 72 | 9.9 ± 7.1 | 12 | 91.7 | 16.1 ± 10.5 |
| 4. Bowel preparation | | | | | | | | | |
| Baseline | 40 | 50.0 | 13.8 ± 13.0 | 23 | 52.2 | 18.0 ± 14.6 | 17 | 47.1 | 7.6 ± 6.8 |
| At colonoscopy | 14 | 14.3 | 2.4 ± 0.4 | 7 | 14.3 | 2.8 | 7 | 14.3 | 2.1 |
| At surgery | 4 | 25.0 | 1.4 | 1 | | 1.4 | 3 | — | — |

*Mean ± standard deviation. Values for methane producers only.

enon (2, 3, 5, 8, 15). In our study two of 23 methane producers became nonproducers on restudy after one year or more. A slight inconsistency in methane production or nonproduction has also been noted by Pitt et al (2), Zucatto et al (8), and Bjorneklett et al (3). This inconsistency should always be remembered when trying to evaluate the effect of potential factors on methane production.

Methanogens have a cell wall devoid of peptidoglycan. They are resistant to a variety of antibiotics acting by different mechanisms. Culture media for their isolation contain antibiotics (17), and it is thus logical to assume that human methane production would not be affected by antibiotic treatment. Theoretically methanogenesis could be affected via suppression of the colonic flora, thus decreasing the amount of a substrate vital to the methanogens or affecting the redox potential of their environment. There are few data in the literature on the effect of antibiotics on methane production in humans. Bjorneklett et al (16) studied seven methane-producing subjects before and after four days of antibiotic therapy. Two patients receiving metronidazole became methane nonproducers, whereas five subjects receiving penicillin or doxycyclin remained producers. Bond et al (5) reported that 37 hospitalized subjects on antibiotics produced methane in a proportion similar to controls. The type and length of treatment were not mentioned. In our study, six of 30 patients on a variety of antibiotics became nonproducers. This is a proportion twice higher than expected, on the basis of restudied controls. Only the combination gentamycin + cefazolin seemed more potent in this regard (three of eight patients). Among our methane nonproducers only three of the 30 CD patients and three of 35 UC patients received metronidazole. None of our IBD methane producing patients received metronidazole. The published data are thus scarce; however, it is possible that some antibiotics affect methane production.

Mechanical bowel cleansing in preparation to colonoscopy or surgery removes the bulk of bacterial flora, and the virtual disappearance of methane production is thus logical. This has been found by us and by others (10, 18). It is interesting to note the differences and similarities between the hydrogen-producing and methanogenic flora. Both are affected by mechanical cleansing of the bowel (19); however, antibiotics affect hydrogen production (13) but have little or no effect on methane production.

It has now been conclusively demonstrated that methane production is affected by gastrointestinal diseases—it is markedly increased in cystic fibrosis and decreased in CD. The status of methane production is still unclear in colonic cancers or precancerous lesions, in UC, and possibly other disorders.

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