Intraluminal pH of the human gastrointestinal tract

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1. INTRODUCTION

The recent and increasing interest in the pH of the contents of the gastrointestinal tract is well founded. One reason is the development of several oral preparations which release the drug at a site and/or at a rate determined by the pH of the surrounding fluid (1-10). Precise knowledge of the pH profile of the gut, including the interindividual variability, is a prerequisite for designing optimal delivery systems based on this concept.

From a theoretical point of view the intraluminal pH of the gut primarily is determined by three factors: the absorption and secretion of acid and base by the intestinal epithelium, the bacterial degradation of ingested food, and the rate of transport of the intestinal contents through the gut.

Determinations of the intraluminal pH of the gastrointestinal tract have been performed for several decades. Early studies were based on aspiration of gastric or intestinal fluids, or measurements on faeces. However, the development of small pH-sensitive, radiotransmitting capsules has provided a method which allows pH-determination under almost physiological conditions.

The aims of the investigations (11-15) presented in this review were as follows: to evaluate a method of determining local intraluminal pH of the gut based upon the combined use of pH-capsules and fluoroscopy; to use this method in studying the pH-profile of the gastrointestinal tract in healthy human subjects and in children; to study the effect of various factors on this pH-profile.

The present review discusses current knowledge of the intraluminal intestinal pH with special reference to data generated with pH-capsules.

2. METHODS

pH of the gut is a very sensitive parameter, influenced by many kinds of outside impacts. A major problem in measuring gastrointestinal pH is, therefore, that it involves the introduction of a tube or a transducer into the gut of the subject studied, and the procedure in itself might induce changes in the pH it measures. Various methods have been developed with the intend to minimize the physical trauma to the subject, thereby minimizing the possible effect of the procedure on the recorded pH.

2.1 INTUBATION TECHNIQUES

Naso-intestinal intubation techniques are easily performed, but pose a number of limitations that can provide less than accurate results. For example, hypersalivation caused by the intubation may dilute the aspirate and thereby raise the gastric pH due to the alkaline pH of saliva. Reflux through the pyloric sphincter due to nausea caused by the procedure may also falsely raise the gastric pH. Conversely, gastric fluid transported along the tube may falsely decrease the pH in the small intestine.

2.1.1 Aspiration technique

Aspiration of gastric fluids through catheters has been employed for decades, and it has the advantage of direct measurement on the fluid. Only the proximal gastrointestinal tract is usually studied by this technique, but *Barbero et al* (16) studied the entire intestinal tract – from the stomach to the rectum – of infants (aged two weeks to three months) by an aspiration technique using an infant Miller-Abbott tube with a balloon inflated with 5-8 ml air. The balloon was inflated when the tube was placed in the duodenum. The tube then passed rapidly to the terminal ileum, and more slowly, within 24-36 hours, through the colon to the rectum. The ethical aspects of performing this potentially hazardous procedure in infants are mentioned in their article.

2.1.2 Dialysis bags

A method introduced by *Marner* (17), later described and utilized by *Rune and Køster* (18) involved the use of a suitable membrane filled with distilled water and placed in the stomach via a connecting tube. After a time the contents of the bag were withdrawn, and the hydrogen-ion content was determined. This method is useful in determining an average pH level in the stomach, but does not reflect rapid changes in gastric pH.

2.1.3 Electrodes

Intubated glass electrodes or antimony electrodes may be used to determine the intraluminal pH of the upper gastrointestinal tract. Electrodes have the advantage over dialysis bags and aspiration techniques that they are capable of reflecting pH fluctuations occurring in the gut lumen. Furthermore, registrations can be made continuously on ambulant patients when the electrode is connected to an ambulatory recording system. *Savarino et al* (19) found an excellent correlation between values obtained with an intragastric pH monitoring equipment (Digitrapper 6000, Synetics, Sweden) and simultaneous gastric aspiration.

2.2 TUBELESS TECHNIQUES

2.2.1 Chemical methods

Indirect methods of determining the presence or absence of gastric acidity have been suggested. One method involved the use of cationic exchange resins to determine the absence or presence of free hydrochloric acid. The procedure depends on the dissociation of the resin by the hydrochloric acid in the stomach. The cation is absorbed and excreted in the urine in the presence of free acid only (20).

Another technique involves the use of pills containing methylene blue wrapped in an indigestible sac tied by a catgut suture. Free acid, if present in the stomach, dissolves the suture and allows the release of the dye. The dye is then absorbed and excreted in the urine. Lack of free acid prevents the release of the dye. This procedure (Desmoid pill technique) was first devised by *Sahli* in 1905 and reintroduced by *Levere and Palmer* in 1960 (21).

Obviously, these methods are indirect, nonspecific, time consuming, and consequently of limited value.

2.2.2 Radiotelemetry capsules

In 1957 the first radiotelemetry capsule for measuring pH was invented by *Jacobsen and MacKay* (22). A copolymer resin, which changed its dimensions with changes in pH, was used as the transducer. The change in dimensions was transferred to an iron core moving inside a coil, and this caused a shift in the frequency of the oscillator in the capsule. The very slow response time of the transducer decreased the clinical value of the capsule, and there are no reports of its use for clinical investigations. In 1959 a telemetry capsule using an antimony electrode as transducer was developed by *Nöller* (23), and this pH-capsule was later referred to as the Heidelberg capsule. The pH measuring cell in the Heidelberg capsule is made up of an annular external antimony electrode which is in contact with the surrounding fluid, and an internal AgCl electrode separated by a semipermeable membrane (24). pH changes the potential difference between the electrodes, which in turn control the frequency of the radio transmitter. The main disadvantages with the early type of this capsule were the short life and serious drift problems, caused by an oxidation of the antimony electrode in the presence of intestinal fluids (25, 26). The limitations of this capsule made it suitable only for studies of the stomach and small intestine, although *Arullani et al* (27) used it in a study of the entire gastrointestinal tract in human vol-

unteers and patients. The study subjects initially passed a tube throughout the gastrointestinal canal and then the capsule was pulled through. Later improvement of the capsule has made it a more reliable tool of pH measurement, but the accuracy of the capsule is still only about 0.5 pH units (28, 29), and the lifetime is only 22 h (29). In 1965-6 two pH capsules using glass electrodes were designed: a Japanese capsule (30), which, however, has never later been mentioned in clinical studies, and a capsule manufactured by Remote Control Systems Ltd, London, England, referred to in the present paper as the RCS capsule (31). The main problem with the pH glass electrode is the high impedance. The electrode must also be sealed to prevent development of leakage paths, which shunt the potential produced by the transducer. The early RCS capsule depended on epoxy resins to form the seal, but moisture caused a gradual deterioration in the pH response and a short lifetime for these capsules. Later a covering layer of glass was added which increased the lifetime of the capsule to more than one month (32). The Japanese capsule and the RCS capsules respond to alterations in pH by changing the transmission frequency of the transmitter in the capsule. The RCS capsule uses a FM oscillator with a transmission frequency of approximately 400 kHz, whereas the transmission frequency of the Japanese capsule is 1.9 MHz. The electrical circuits of the two capsules share many aspects. A glass pH-electrode is in contact with the surrounding fluid and an Ag/AgCl reference electrode is situated in the battery cap of the capsule. Variation in potential difference between the pH-electrode and the reference electrode causes a change in the capacitance of a reverse biased diode (varicap), with a corresponding change in output frequency (32, 33). The response in transmission frequency of the RCS capsule is linear in the interval between pH 1 and pH 9 (33, 34).

A small number of other types of radiotelemetry pH-capsules have been developed but the Heidelberg capsule and the RCS capsule (Fig. 1) are those most frequently used in published clinical studies.

2.2.2.1 Methodological problems using the pH-capsule

a. *Localization of the capsule*

When an untethered capsule is ingested, it travels freely throughout the gastrointestinal canal, and a crucial point is how to determine the precise location of the capsule in the gut at the time of pH measurement. The location which poses most problems is the ileo-caecal region. By using a radio directional antenna to determine the position at which the maximum signal strength of transmission is received, the regional localization of the capsule can be made with an accuracy of 5 cm (35, 36), but it is not possible to determine by this method whether it is located in the caecum or in the terminal ileum. Fluoroscopy enables a more precise localization, but if the gas content of the colon is sparse, the distinction between the terminal ileum and the caecum may be difficult. The use of radiopaque contrast (15) or gamma scintigraphy technique (35) to visualize the region may be an advantage. Repeated fluoroscopic investigations with short intervals in between can be of great help, especially when sudden changes in pH occur. It is often observed that a capsule located in the ileocaecal region has dropped 5 to 10 cm downwards (i.e. into the caecum) between two fluoroscopic investigations, and usually this is associated with a sharp decrease in pH. However, it must be recognized that even with the use of frequent fluoroscopic determinations of the location of the capsule, and even with the assistance of a skilled radiologist, a small number of the determinations may be incorrect. The major problem with repeated fluoroscopic investigations is the radiation exposure. The length of radiation must be kept as short as possible, and this may best be achieved with the collaboration of a radiologist.

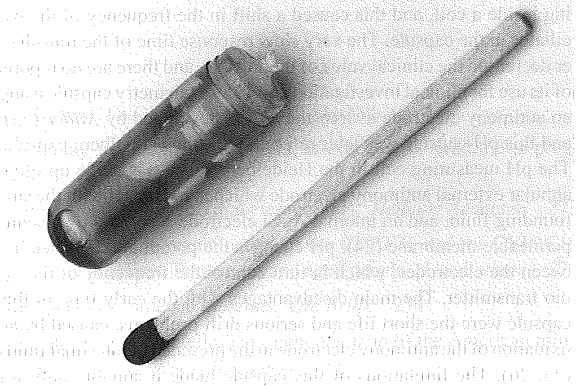

Fig. 1. *The pH-sensitive, radiotelemetry capsule (RCS capsule). Dimensions: diameter 7 mm, lenght 27 mm (a match is shown for comparison of size).*

An improved method of localisation of the pH-capsule in the caecum was used by *Sasaki et al* (37). A contrast colonogram was obtained before the investigation. The receiver was connected to a computer-assisted analysing system, and when pH sharply decreased by 1 pH unit/min or more (i.e. when the capsule entered the caecum) the system generated a beeping sound. A plain abdominal x-ray was performed and superimposed on the previously performed contrast colonogram, and the presence of the capsule in the caecum could be verified. Thereafter, the position of the capsule in the colon was determined at 2-h intervals with a radio directional antenna. In two patients a plain x-ray film was taken after a measurement of pH by the antenna, and the position of the capsule judged by the antenna method was correct. The study demonstrates, that if the configuration of the colon is known, the localization of the capsule can be reasonably well determined by the use of a radio directional antenna. The method is elegant and the computer-assisted analysing system could be of great help in monitoring pH in the colon of patients with chronic inflammatory bowel disease, where very low pH values have been reported (14). However, a contrast colonogram may not be available in all patients, and the topographic position of the colon may be slightly influenced by the position (upright or succumb) of the patient.

b. *Gastrointestinal transit of the capsule*

When the capsule is ingested, it is freely mobile and its localization in the gut will be determined by the propulsion movements of the gastrointestinal myometrium. The gastric emptying of large (>1 mm) particles is dependent on the interdigestive migrating myoelectric complex (IMMC) (38, 39). When solid food is present in the stomach it contracts 3-4 times per minute, and the pylorus is partially opened, allowing liquid and small particles to pass. When the stomach is empty of food, several phases of myoelectric activity occur, ending with the phase III, the IMMC, which consists of an opening of the pylorus and of 3-4 peristaltic contractions from the stomach to the caecum, allowing emptying of the stomach of undigested material ("the housekeeper wave") (40, 41). This cyclic pattern of events occurs on average every two hours in fasting humans, but it is interrupted when food is ingested. The gastric residence time (GRT) of the pH-capsule therefore depends on the dietary state of the subject. In a fasting subject the average GRT of the capsule is 1.1 to 1.9 hours (11-13, 29, 42). A small liquid meal prolongs the mean GRT to 2.6 hours, and frequent intakes of food increases it to more than 14.5 hours (42). This important aspect concerning the gastric emptying must be taken into account when sustained release tablets with coatings resistant to acid are prescribed. If such tablets are taken together with meals, they will remain in the stomach until it is empty of food, and if the subject eats frequent meals during the day the stomach will not be empty before sometime during the night. Consequently, it is of no relevance to take such tablets two or more times daily, while all or most of the tablets will remain in the stomach the entire day and later all are emptied into the duodenum sometime during the following night (43, 44).

The small intestinal transit time (SITT) of the capsule in adults varies from 2.8 to more than 14 hours (11, 45) and average values of 5.7 to 8 hours are reported (11, 35). The capsule travels rapidly from

the duodenum to the distal part of the small intestine, and about two-thirds of the SITT is spent in the part of the small intestine that is located in the lower right abdominal quadrant (11). This slow transit through the distal small intestine is in accordance with the observation of *Kerlin & Phillips* (46), who found that the IMMC travels through the small intestine with a velocity that decreases from 4.7 cm/min in the jejunum to 0.9 cm/min in the terminal ileum. Ingestion of food also interrupts the IMMC of the small intestine (46). In children, the median SITT was almost identical to that of adults (7.5 hours), and for three quarters of that time the capsule is located in the distal small intestine (13). The rapid transit through the jejunum makes it difficult to study the pH of this part of the gut with a freely moving pH capsule. In a study using capsules tethered with a 2 metres long nylon line it was possible to obtain pH measurements from the proximal part of the jejunum (34). However, the line slowed the transit of the capsule considerably, so it was not possible to measure pH in the more distal parts of the small intestine in that study.

The colonic transit time of the capsule is about 17.5 hours (equal in adults and children), but it varies widely from less than 10 hours to 112 hours, and the capsule is located in the caecum for about half of this time (11, 13). The colonic transit time tends to be longer in females than in males (11).

The day-to-day variation of the regional transit times is considerable, and in a study of the day-to-day variation in 13 healthy subjects the variation coefficients of the GRT and colonic transit time were about one (11). The SITT was more consistent and the variation coefficient was 0.40 (11).

c. *Linearity, frequency drift, precision and accuracy*

The response of the transmission frequency to alterations in pH was tested by *Meldrum et al* (33) and by *Fallingborg et al* (34) concerning the RCS capsule, and was found to be linear within the interval between pH 1 and pH 9. The response of the Heidelberg capsule has also been found to be linear in the interval between pH 2 and 7, but above and below this interval the frequency response decreased (47). Calibrations of the capsules before and after a study will secure their accuracy at the calibration levels at the beginning and at the end of the study. As previously mentioned, the main problem with the early types of radiotelemetry capsules, and especially the Heidelberg capsule, was the frequency drift. This was mainly due to an oxidation of the antimony electrode in the presence of intestinal fluids. The problem was less with capsules using glass electrodes, and in the study of *Fallingborg at al* (11), using the RCS capsule, a maximal drift of 0.5 pH units was registered, with the exception of one subject in whom the increased drift was due to a defective reference cap. The frequency drift may affect both the accuracy (zero-point drift) and the precision (change of the slope of the response-curve) of the pH capsule, but, assuming that the drift develops with a constant rate during the study, a correction of the frequency drift can be performed after recalibration of the recovered capsule (14):

$$pH_{Tx} = 1 - 8 \times \frac{\tilde{O}_{Tx} - \tilde{O}_{pH1(To)} - \frac{T_x - T_o}{T_{end} - T_o} \times (\tilde{O}_{pH1(To)} - \tilde{O}_{pH1(Tend)})}{\tilde{O}_{pH1(To)} - \tilde{O}_{pH9(To)} - \frac{T_x - T_o}{T_{end} - T_o} \times (\tilde{O}_{pH1(To)} - \tilde{O}_{pH1(Tend)} - \tilde{O}_{pH9(To)} - \tilde{O}_{pH9(Tend)})}$$

pH_{Tx}:	Corrected pH value, measured at T_x
T_o:	Time of pre-calibration
T_{end}:	Time of post-calibration
T_x:	Time of pH measurement
$\tilde{O}_{Tx}$:	Transmission frequency measured at time T_x
$\tilde{O}_{pH1(To)}$:	Transmission frequency of the capsule at pH1, 37°C, measured at pre-calibration
$\tilde{O}_{pH1(Tend)}$:	Transmission frequency of the capsule at pH1, 37°C, measured at post-calibration
$\tilde{O}_{pH9(To)}$:	Transmission frequency of the capsule at pH9, 37°C, measured at pre-calibration
$\tilde{O}_{pH9(Tend)}$:	Transmission frequency of the capsule at pH9, 37°C, measured at post-calibration

The accuracy of the RCS capsule has been evaluated by *Meldrum et al* (33) and by *Fallingborg et al* (12) by comparing pH in faeces and ileostomy output, measured by the RCS capsules and with a pH-meter (Radiometer, Copenhagen), respectively. The maximal difference between pH values measured with the two methods was 0.2 and 0.3 pH units, respectively, in the two studies.

d. *Frequency of measurements*

In some studies pH was automatically registered 6 or 60 times per minute and stored in a recording system, whereas in other studies including those made by the author of this thesis the measurements were performed manually with intervals of 10 minutes or more. The frequent, automatic recording method has several advantages: it can be used in outpatients, it is able to demonstrate pH-changes of short duration, and measurements can also be performed while the person sleep. The major disadvantages of this system are that only one subject can be studied at a time for each recording system, and that measurements obtained during periods with low signal or signal loss may be incorrect. The importance of a high signal quality was emphazised by *Press et al* (48) who observed that artificial low pH values could be registered when the recorder indicated poor signal quality. The main advantage with manual recording is that an optimal signal quality can be secured at each recording, and that more than one subject can be studied at the same time. The disadvantages are that pH-changes that occur between measurements will not be discovered, and that the method cannot be used in outpatients.

3. GASTROINTESTINAL pH IN NORMAL HUMAN SUBJECTS

Since 1964 a number of studies on human gastrointestinal pH using pH-sensitive capsules have been published. The majority of these studies deal with measurements of gastric residence time or measurements of the acid secretory capacity of the stomach, and, therefore, only contain pH measurements from the stomach and the duodenum (Table 1). However, a number of studies also report pH measurements from more distal parts of the gut (Table 2). Many papers contain data obtained from normal human subjects, but in several of

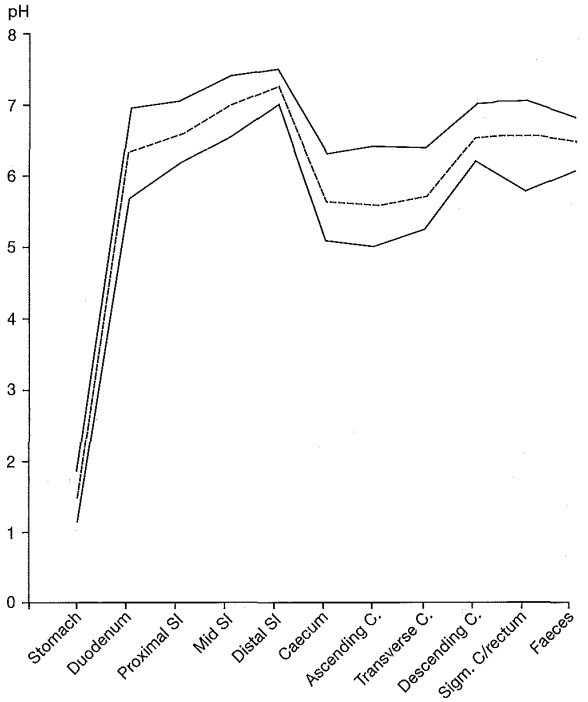

Fig. 2. *Median (broken line) and interquartile range of gastrointestinal pH measured in 33 healthy, adult volunteers (11).*

Table 1. *Published studies on the use of pH-sensitive, radiotransmitting capsules. In vitro studies and human studies confined to measurements in the stomach and/or in the duodenum.*

References	Type of capsule	Subjects
Jacobson & MacKay, 1957 (22)	prototype, 400 kHz	–
Nöller, 1959 (23)	prototype, 1.9 MHz (Heidelberg)	–
Connel & Waters, 1964 (25)	Heidelberg	30 duodenal ulcer patients
Steinberg et al, 1965 (47)	Heidelberg	–
Watson & Patton, 1965 (49)	Heidelberg	30 normal subjects and patients
Ranft & Nöller, 1965 (50)	Heidelberg	50 normal subjects (+ antacids)
Watson & Kay, 1965 (31)	prototype, 400 kHz (RCS)	–
Stavney et al, 1966 (51)	Heidelberg	20 duodenal ulcer patients
Kuhn et al, 1966 (52)	Heidelberg	18 patients with dystrophia myotonica
Nöller, 1967 (53)	Heidelberg	46 dyspectic patients (+ Spasmo-Nervogastrol®)
Stilliger, 1967 (54)	Heidelberg	12 patients (+ metoclopramide)
Maiwald et al, 1967 (55)	Heidelberg	Cases
Kütter, 1967 (56)	Heidelberg	Cases
Aynaciyan & Bingham, 1969 (26)	Heidelberg	24 normal subjects, 22 duodenal ulcer patients
Yarbrough et al, 1969 (24)	Heidelberg	26 patients
Deyhle et al, 1969 (57)	Heidelberg	29 patients
Williamson et al, 1969 (58)	Heidelberg	45 patients with anaemia (21 with pernicious anaemia)
Stack, 1969 (59)	Heidelberg	1 normal subject and 29 patients
Russell & Goldberg, 1970 (60)	Heidelberg	23 dyspeptic patients (+ acetysalicylic acid)
Goldstein & Packman, 1970 (61)	Heidelberg	13 normal subjects (+ antacids)
Andres & Bingham, 1970 (62)	Heidelberg	27 dyspeptic patients
Kuntz et al, 1971 (63)	prototype, 1.9 MHz	Cases
Jóhannesson et al, 1973, (64)	Heidelberg	10 duodenal ulcer patients
Sadchikova, 1973 (65)	Heidelberg	37 healthy children
Madee & Müller-Wieland, 1975 (66)	Heidelberg	16 normal subjects (+ antacids)
Kotter et al, 1975 (67)	Heidelberg	23 normal subjects (transcranial electrotherapy)
Truchaud et al, 1975 (68)	Heidelberg	118 normal subjects (+ antacids)
Ekenved & Walan, 1975 (69)	Heidelberg	10 normal subjects (+ antacids)
Stacher & Starker, 1975 (70)	Heidelberg	5 normal subjects (+ insulin ± bromazepam)
Misaki & Kawai, 1976 (71)	2 prototypes	4 normal subjects + 19 peptic ulcer patients
Ritschel & Erni, 1977 (72)	Heidelberg	12 normal subjects
Heinkel, 1980 (73)	Heidelberg	147 patients
McGraw et al, 1981 (74)	Heidelberg	11 normal subjects (+ sucralfate / + antacids)
Uusitalo & Keyrilainen, 1983 (75)	Heidelberg	24 normal subjects, 31 duodenal ulcer patients.
Puch et al, 1984 (76)	Heidelberg	10 normal subjects (+ antacids)
Mojaverian et al, 1985 (42)	Heidelberg	16 normal subjects
Faegenburg et al, 1985 (77)	Heidelberg	1 patient with Crohn's disease
Reynolds et al, 1986 (78)	RCS	4 duodenal ulcer patients
Rocci et al, 1987 (79)	Heidelberg	8 normal men (+ procainamide)
Mojaverian et al, 1987 (80)	Heidelberg	8 normal subjects (+ aspirin)
Mojaverian et al, 1988 (81)	Heidelberg	45 normal subjects
Ewe et al, 1989 (82)	Heidelberg	10 normal subjects
Mojaverian et al, 1990 (83)	Heidelberg	12 normal men (± ranitidine)
Chan et al, 1990 (84)	Heidelberg	8 healthy men (+ diclofenac sodium)
Mojaverian et al, 1991 (29)	Heidelberg	4 normal subjects
Piscitelli et al, 1991 (85)	Heidelberg	6 normal males (+ ketoconazole ± cimetidine ± sucralfate)
Knapp et al, 1991 (86)	Heidelberg	6 normal subjects (+ glutamic acid ± ranitidine)
Betlach et al, 1991 (87)	Heidelberg	12 normal subjects (+ theophylline ± ranitidine)
Lebsach et al, 1992 (88)	Heidelberg	12 normal subjects (+ enoxacin ± ranitidine/pentagastrin)
Russell et al, 1993 (89)	Heidelberg	79 healthy elderly subjects
Meyer et al, 1993 (90)	Heidelberg	8 normal subjects, 7 achlorhydric subjects. (+ theophylline)
Alioth et al, 1993 (91)	Heidelberg	18 normal subjects (+ diclofenac ± ranitidine)
Zimmermann et al, 1994 (92, 93)	Heidelberg	24 normal subjects (+ fluconazole or itraconazole)
Russell et al, 1994 (94)	Heidelberg	11 healthy subjects (> 64 years, + dipyridamole ± famotidine)
Zimmermann et al, 1994 (95)	Heidelberg	12 normal subjects (+ fluconazole ± omeprazole)
Henderson et al, 1995 (96)	Heidelberg	10 normal subjects (+ zinc acetate or zinc oxide ± famotidine)
Groning & Berntgen, 1996 (97)	Heidelberg	5 normal subjetcs
Lewis & Heaton, 1997 (98)	?	13 normal subjects

these articles the results from the healthy subjects and those obtained from patients are not separated. Therefore, only a limited number of these study results can be used to describe the pH-profile of normal humans (Table 3). On the basis of these selected studies, supplemented with results from studies using other methods, a picture of the pH profile of the normal gastrointestinal tract can be made. However, it should be kept in mind that a normal colonic pH-profile may vary in different ethnic and cultural groups and in different parts of the world, because dietary habits may affect the intraluminal pH (see Chapter 7.1).

The pH-profile of the normal gastrointestinal tract, based on measurements obtained with the RCS capsule, is shown in Fig. 2 (11).

3.1 STOMACH

The acid environment in the lumen of the stomach is attained by proton secretion from the parietal cells in the corporal mucosa. In a fasting subject, the pH of the gastric fluid ranges from 1 to 3.5 (11, 27, 30, 89), but ingestion of food, milk, or antacids may shortly increase pH to about 7 (24, 33, 89, 110).

3.2 DUODENUM

Due to the rapid transit of the untethered pH capsule through the duodenum, only a few recordings can be performed in this region using this method. Thus, results obtained with tubes, glass electrodes, or tethered capsules must be regarded as the most reliable. In the duodenum, the pH of the intestinal fluid is changed from acid to neutral

Table 2. *Clinical studies on human gastrointestinal pH measured with pH-sensitive, radiotransmitting capsules. Studies containing pH measurements in the small intestine and/or in the colon.*

References	Type of capsule	Region	Subjects
Watson & Paton, 1965 (49)	Heidelberg	jejunum	1 normal subject and 16 patients (secretin)
Kitagawa et al, 1966 (30)	prototype, 1.9 MHz	Total GI-tract	20 normal subjects and patients
Arullani et al, 1967 (27)	Heidelberg	Total GI-tract	9 normal subjects, 10 patients
Maxwell et al, 1971 (99)	Heidelberg	jejunum	10 normal subjects, 21 patients
Meldrum et al, 1972 (33)	RCS	Total GI-tract	2 normal subjects, 7 patients
Palva et al, 1972 (100)	Heidelberg	Ileum	21 patients receiving potassium
Bown et al, 1974 (101)	RCS	Total GI-tract	11 normal subjects (±cathartics)
Colson et al, 1981 (32)	RCS	Upper GI-tract	cases
Evans et al, 1986 (102)	RCS	Colon	23 normal subjects, 21 colonic neoplasia patients
Patil et al, 1987 (103)	RCS	Term. ileum, colon	6 normal subjects (±lactulose/lactitol)
Hardy et al, 1987 (6)	RCS	Stomach, SI, caecum, c. asc.	6 normal subjects (+naproxen)
Pye et al, 1987 (104)	RCS	Colon	8 normal subjects (±dietary fibers)
Youngberg et al, 1987 (28)	Heidelberg	Stomach and SI	10 normal subjects, 10 patients with cystic fibrosis
Evans et al, 1988 (35)	RCS	Total GI-tract	66 normal subjects
Gilbert et al, 1988 (105)	RCS	Stomach and SI	42 normal subjects, 6 patients with cystic fibrosis
Mojaverian et al, 1989 (45)	Heidelberg	Stomach and SI	6 normal males
Fallingborg et al, 1989 (11)	RCS	Total GI-tract	33 normal subjects
Pye et al, 1990 (36)	RCS	Total GI-tract	66 normal subjects, 67 colonic neoplasia patients
Fallingborg et al, 1990 (12)	RCS	Stomach and SI	11 healthy ileostomates
Fallingborg et al, 1990 (13)	RCS	Total GI-tract	12 normal children
Hardy et al, 1991 (8)	RCS	Stomach + SI	8 normal subjects (+naproxen)
Raimundo et al, 1992 (106)	RCS	Total GI-tract	7 normal subjects, 13 patients with ulcerative colitis
Wyeth et al, 1992 (107)	RCS (?)	Colon	8 normal subjects, 13 colonic neoplasia ptt. (±dietary fibers)
Fallingborg et al, 1992 (108)	RCS	Total GI-tract	12 normal subjects (+Pentasa®±cimetidine)
Zimmerman & Leitold, 1992 (109)	Heidelberg+Flexilog 1010	Stomach and SI	24 normal subjects
Fallingborg et al, 1993 (14)	RCS	Total GI-tract	7 patients with ulcerative colitis
Fallingborg et al, 1994 (34)	RCS	Duodenum, jejunum	13 normal subjects (±Pentasa®/Dipentum®)
Press et al, 1996 (48)	RCS	Total GI-tract	12 Crohn's, 11 ulcerative colitis, 12 normal subjects
Sasaki Y et al, 1997 (37)	RSC	Total GI-tract	4 normal subjects, 4 patients with Crohn's disease
Fallingborg et al, 1998 (15)	RSC	Stomach, SI, proximal colon	9 ileo-caecal resected Crohn's patients, 13 normal subjects

Table 3. *Median or mean gastrointestinal pH-levels of normal, adult human subjects measured by pH-sensitive, radiotransmitting capsules.*

References	N	Stomach	Duodenum	Proximal SI	Mid SI	Distal SI	Caecum	Asc. c.	Transv. c.	Right c.	Desc. c.	Sigm/rect	Left c.
Arulani et al, 1967 (27)	9	1.7	5.66	6.49	7.06	7.52	7.70	7.71	8.16	–	8.66	8.66	–
Maxwell et al, 1971 (99)	10	–	–	5.5-6.5	–	–	–	–	–	–	–	–	–
Bown et al, 1974 (101)	11	–	–	5.9	6.8	7.5	–	–	–	6.0	–	–	6.8
Evans et al, 1986 (102)	23	–	–	–	–	–	–	–	–	6.2	–	–	6.75
Patil et al, 1987 (103)	6	–	–	–	–	7.51	–	–	–	6.51	–	6.53	–
Pye et al, 1987 (104)	8	–	–	–	–	–	–	–	–	6.5	–	–	7.3
Gilbert et al, 1988 (105)	42	–	–	6.61	–	7.50	6.37	–	–	–	–	–	–
Evans et al, 1988 (35)	66	1.75	–	6.63	7.41	7.49	–	–	–	6.37	–	–	7.0
Fallingborg et al, 1989 (11)	33	1.4	6.4	6.6	7.0	7.3	5.7	5.6	5.7	–	6.6	6.6	–
Mojaverian et al, 1989 (45)	6	–	–	–	–	7.3	–	–	–	–	–	–	–
Raimundo et al, 1992 (106)	7	–	5.8	6.6	–	7.4	–	–	–	6.7	–	–	–
Wyeth et al, 1992 (107)	8	–	–	–	–	–	–	–	–	5.70	–	–	6.01
Fallingborg et al, 1994 (34)	13	–	6.22	6.06	–	–	–	–	–	–	–	–	–
Press et al, 1996 (48)	12	–	–	6.7	–	7.4	6.0	–	–	6.0	–	–	6.2
Sasaki et al, 1997 (37)	4	1.4	–	6.8	–	7.7	–	–	–	6.8	–	–	7.2
Fallingborg et al, 1998 (15)	13	1.4	–	6.4	7.1	7.4	–	–	–	5.8	–	–	–

within a distance of a few centimetres. pH increases from 2 to 5 within the proximal 10 cm of the duodenum, but very large fluctuations in pH of the proximal duodenum are observed due to the peristaltic emptying of gastric fluid through the pylorus (110). These fluctuations diminish in the distal parts of the duodenum and the mean pH further increases to about 6 (110). The mean duodenal pH reported in a study using tethered capsules was 6.22 (34), and in studies using untethered capsules mean pH values ranges from 5.66 to 6.4 (11, 27). The difference in duodenal pH measured with tethered and untethered capsules may be due to the rapid passage of an untethered capsule through the duodenum. The rapid passage in combination with the calibration time of the pH-capsule (approximately 2 seconds (30)) probably make the measurements with tethered capsules more reliable. The alkalization of the intestinal contents is due to a secretion of alkaline mucus from the Brunner's glands of the duodenum and to the secretion of bile and pancreatic juice through the Vaterian papilla. Bile is generally slightly alkaline and pancreatic juice has a high concentration of bicarbonate and a pH value of 8.03 (111). The secretion of bile is induced by a stimulation of the secretion of the hormone cholecystokinin by the presence of triglycerides in the duodenum, and the secretion of pancreatic juice is induced by the hormone *secretin* released from cells in the duodenum when the intraluminal pH of the proximal duodenum decreases to below pH 3-4 (112).

3.3 SMALL INTESTINE

The pH of the proximal part of jejunum also is most easily and reliably measured using tubes, electrodes, or tethered capsules. Median pH levels from 4.92 in fasting subjects to 6.08 during the first hour after a meal have been measured by aspiration of fluid at the duodeno-jejunal junction (110). Using tethered capsules, a mean pH value of 6.06 was found in fasting subjects (34). Although there was no statistically significant difference between proximal jejunal pH and duodenal pH in the two studies, pH of the proximal jejunum tended to be slightly lower than that of the duodenum. This agrees with the results of studies demonstrating that an acidifying process caused by absorption of bicarbonate occurs in the proximal jejunum (113, 114).

The first publication on pH of the entire gastrointestinal tract using pH capsules was by *Kitagawa et al* (30) in 1966, but no exact values

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