



Sveriges lantbruksuniversitet  
Swedish University of Agricultural Sciences

Faculty of Natural Resources and  
Agricultural Sciences  
Department of Food Science

## **B 221 - Marathoner's cure for bowel related problems?**

- Double blind, placebo controlled study of egg powder B 221 in reducing disturbances in the gastrointestinal tract during long distance running

*Martin Köhlerstrand*

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B 221 in reducing disturbances in the gastrointestinal tract during long distance running

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## Abstract

A double blind, placebo-controlled and randomized study was conducted at Stockholm Marathon 2011. The aim was to investigate if egg yolk powder B 221 with high levels of Antisecretory factor could decrease the prevalence of diarrhea among runners that had experienced diarrhea at >50% of their marathon races. The study did not reach the planned number of 200 study subjects and also encountered problems with dropouts. The number of study subjects was 55 on the day of the marathon. There was no significant difference between placebo and active treatment ( $p=0.23$ ). The prevalence of diarrhea was 59% (B 221) and 43% (placebo), respectively. The study could not show that a diet supplemented with B 221 had a decreasing effect on the prevalence of diarrhea in the studied population during the day of the marathon race.

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# 1 Introduction

## 1.1 Gastrointestinal disturbances among runners

Runners are not the only athletes suffering from gastrointestinal disturbances, but runners as a group has been reported peaking in prevalence (Peters, 1999). Table 1 summarizes the findings from four different studies on gastrointestinal disturbances among marathon runners. As seen in Table 1 32 to 42 percent of the respondents experienced a strong urge to defecate when running marathon races. Moreover about 20 percent of marathon runners suffer from diarrhea during, under or after a finished race. Other common problems are heartburn, nausea, vomiting, cramps in the gastrointestinal tract, stomach-ache and side ache (Keeffe *et al.*, 1984; Riddoch & Trinick, 1988; Sullivan & Wong 1992).

Many factors have been suggested for causing the disturbances; mental stress, exhaustion, low blood sugar and increased activity in the sympathetic nervous system, hence affecting the gastrointestinal system are some examples. As the intensity of the physical activity increases more blood is redirected from the gastrointestinal system to the muscles, which could lead to a decreased function (Baska *et al.*, 1990; Sawka & Young, 2005). Another potential factor for diarrhea is intracellular disturbances in electrolytes as a result of endurance exercise, hence leading to decreased smooth muscular and mucosal function (Keeffe *et al.*, 1984).

Table 1. Percentage of long distance runners reporting different gastrointestinal symptoms in four different studies.

Symptom/Study	Keefe <i>et al.</i> , 1984.	Riddoch & Trinick, 1988.	Rehrer & Janssen, 1989.	Sullivan & Wong, 1992.
Loss of appetite (%)	-	28	-	-
Heartburn (%)	10	13	-	24
Nausea (%)	12	20	11	-
Vomiting (%)	2	4	-	-
Abdominal Cramps (%)	19	31	-	35
Urge to defecate (%)	37	42	-	-
Diarrhea (%)	19	27	0	-
Stomach ache (%)	-	-	25	-
Side ache (%)	-	-	23	-
Intestinal cramps (%)	-	-	18	-

Yet another factor that might influence the prevalence of diarrhea among runners are sport drinks and sport gels with a carbohydrate level from 7-10% and above. When these products are consumed the high carbohydrate level in the gut will, by osmosis, draw fluid into the colonic tract, resulting in diarrhea or an urge to defecate (Rehrer & Janssen, 1989).

## 1.2 Antisecretory factor, Special processed cereals, and B 221

In 1987 Ivar Lönnroth and Stefan Lange concluded that specific carbohydrates and amino acids have a positive effect on the endogenous production of the protein Antisecretory factor, AF (Lange & Lönnroth, 1987). AF is a highly preserved protein and can be found in all mammalian species in the most tissues of the body (Lange *et al.*, 1999).

Animal studies have shown an increase of AF production when subjects are exposed to enterotoxins (Lange & Lönnroth, 2001) and in another study AF has been proven to decrease the diarrheal and inflammatory effect of bacterial enterotoxins like cholera toxin which is produced by the bacteria *Vibrio cholerae* (Johansson *et al.*, 1997).

AF has also been seen to inhibit the cytotoxic- and inflammatory action of toxin A. Toxin A is an endotoxin from the gram-positive *Clostridium difficile* species.

Further, the authors suggest that AF might be part of the defense against dehydration and inflammation caused by enterotoxins. It has been suggested that too low levels of AF might be the reason for piglet diarrhea (Lange *et al.*, 1987).

In a study on patients suffering from long-standing symptoms of inflammatory bowel disease, IBD, study subjects were given special processed cereals (SPC) or untreated cereals. SPC are cereals that have been hydrothermally treated in a process that has similarities with malting. The process alters the amounts of sugars and amino acids in the cereals. Table 2 displays the changes in carbohydrate and amino acid composition before and after hydrothermal treatment of the cereals. Study subjects given SPC showed higher levels of AF in their blood than study subjects that had received untreated cereals. Further, study subjects given SPC reported improved ratings of clinical symptom. No significant change in the clinical symptom rating could be seen in the group of study subjects that had been given untreated cereals (Björck *et al.*, 2000).

*Table 2. The change in amounts of 4 types of carbohydrates and 5 types of amino acids per gram of dry matter before and after the specific hydrothermal treatment (Björck et al., 2000).*

	Before hydrothermal treatment (mg/g DM)	After hydrothermal treatment (mg/g DM)
Glucose	0.3–0.4	0.6–5.3
Fructose	0.3–0.4	0.6–3.1
Sucrose	8.4–14.4	36.8–65.7
Maltose	0	4.0–9.0
Histidine	0	0.06–0.25
Glutamic acid	0.12–0.20	0.42–0.44
Lysine	0.03–0.06	0.15–0.29
Tryptophan	0.09–0.22	0.28–0.45
Isoleucine	0	0.05–0.30

AF is a lectin carbohydrate-binding protein that has been shown to have hormone-like properties, with the capacity to regulate water and electrolyte transport in the small intestine and thus been investigated and used in threatening different conditions of diarrhea (Lange *et al.*, 1994).

AF levels may be negatively affected by stress. In an experiment, rats that either were subjected to experimentally induced stress or given an injection of the stress



hormone adrenocorticotropine showed a decrease in AF levels in blood and in the pituitary gland (Ulgheri *et al.*, 2010).

As illustrated in Fig 1, hens that have been fed SPC feedstuff will spawn eggs that contain high amounts of AF in the yolk. The yolk is spray dried and packaged in sachets. The product is named B 221 when used in scientific research (Zaman *et al.*, 2007). B 221 is also marketed under the consumer brand name Salovum®. The product is on the Swedish national list of products for special nutrition / medical purposes (LVFS 2010:27) which is issued by Medical Products Agency Sweden (Läkemedelsverket).

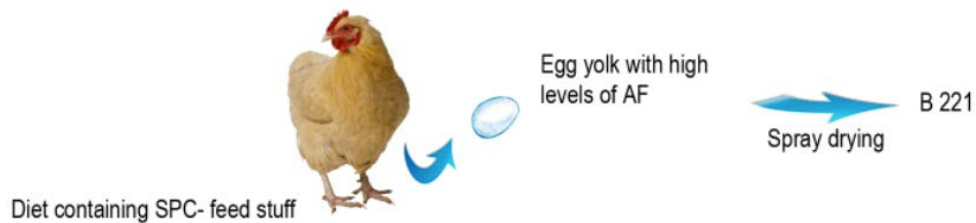


Figure 1. Illustration of how laying hens fed SPC-feed stuff lay eggs rich in AF. Spray drying of these egg yolks results in the egg yolk powder B 221 or Salovum®.

### 1.3 B 221 studies

In a study on acute diarrheal symptoms in children aged 6 to 24 months, subjects who were given anti secretory proteins in concentrated form B 221 showed a significantly faster recovery rate than subjects who were given placebo (Zaman *et al.*, 2007).

A smaller study on endocrine diarrhea, four patients with mid-gut carcinoid syndrome and two with metastasizing medullary thyroid carcinoma, MTC, reported significantly ( $p < 0.01$ ) fewer daily bowel movements when treated with B 221. Daily bowel movements decreased from an average of 5.6 to 4.2. Further, the study reported an increase in formed stools. Before treatment with B 221 started, study subjects recorded the consistency of their stools during one week with a reported number of 14% formed stools. During the last week of a total of 4 weeks treatment with B 221, the reported number of formed stools was 41% (Laurenus *et al.*, 2003).

#### 1.4 AF mode of action

AF interacts with the protein flotillin-1. Flotillin-1 is present in a structure in cell membrane named “lipid rafts”. Lipid rafts are thicker areas of the cell membrane enriched with sphingolipids and cholesterol. Lipid rafts house large protein complexes due to the extra space available. The proteins found in lipid rafts often play a role in intracellular communication pathways; making lipid rafts a common target for viruses and other virulence factors. Cholera toxin (CT) from *Vibrio cholerae* and *Escherichia coli* heat labile toxin (LT) both bind to a ganglioside named GM-1, commonly attached to flotillin-1. When bound, the two toxins activate different signal transduction pathways both resulting in diarrhea. The binding of AF to flotillin-1 has been proposed to alter the characteristics of the lipid rafts. Binding leads to a change in the positions of signal proteins and their receptors, therefore decreasing the effect of toxins that cannot find a binding point (Ulgheri *et al.*, 2010).

#### 1.5 Aim

The aim of this study was to investigate if a diet complemented with egg yolk powder high in Antisecretory factor, AF, could have a reducing effect on the prevalence of diarrhea among runners participating in the Stockholm Marathon which was held on the 28<sup>th</sup> of May 2011.

## 2 Materials and Methods

### 2.1 Ethical approval

The Ethical Review board of Uppsala University approved this study.

### 2.2 Study Population

A total of 5732 runners (74% male, 26% female) were contacted via the Stockholm Marathon register with the use of an e-mail marketing service. Runners who were interested and who judged themselves to meet the inclusion/exclusion criteria were asked to fill in a questionnaire regarding body measurements and their history of gastrointestinal disturbances on the study web-page.

The number of runners that filled in the screening questionnaire was 169 (61% male, 39% female). The answers were reviewed by the study doctor and checked against the inclusion/exclusion criteria in Table 3. The number of runners meeting all criteria and that was intended to be the study population was 103.

*Table 3. The inclusion and exclusion criteria of the study.*

<u>Inclusion criteria:</u>	<u>Exclusion criteria</u>
<ul style="list-style-type: none"><li>• Will participate in the 2011 Stockholm Marathon</li><li>• 18 years old or older</li><li>• Healthy</li><li>• History of gastrointestinal disturbances in connection to running in at least half of total participated races</li><li>• Participated in at least one marathon</li></ul>	<ul style="list-style-type: none"><li>• Chronic gastrointestinal disease</li><li>• Allergic to egg</li><li>• Prone to constipation</li><li>• On a diet with SPC - Flakes</li></ul>

## 2.3 Design

The study design was of the type randomized, placebo controlled and double blind. Study subjects were randomly assigned to two different groups with 50% of the study subjects in each group. The total time of treatment was three days.

Table 4 is showing the demography data of the 55 study subjects that fulfilled the study. The active group consisted of 17 male and 11 female study subjects and the control group consisted of 21 male and 6 female study subjects. The overall composition of study subjects was 78% male and 32% female.

*Table 4. Demography of the 55 study subjects. Range within brackets.*

Gender	Treatment	n	Age (years)	Height (cm)	Bodyweight (kg)
Male	B 221	17	41.2 (26 / 53)	181.2 (159 / 193)	76.6 (57 / 93)
	Placebo	21	40.9 (29 / 65)	182.0 (172 / 195)	79.2 (71 / 88)
Female	B 221	11	39.0 (24 / 58)	169.2 (163 / 175)	60.0 (54 / 71)
	Placebo	6	40.5 (27 / 50)	168.7 (160 / 175)	59.9 (48 / 72)

Calculation of sample size was done using a two-sided Chi-square test at a 0.05 significance level and 80 % power. Results show that at least 82 subjects per group are needed to detect an absolute difference between treatments of 20 percentage points or more. Power calculation was done using Nquery 6.02.

## 2.4 Defining diarrhea

The primary efficacy variable was the prevalence of diarrhea on the day of the race.

The Bristol Scale Stool Form, see Figure 2, is an instrument to classify the form and consistency of stools (Lewis & Heathon, 1997). To be able to classify if study subjects experienced diarrhea or not, the commonly used Bristol Scale Stool Form

was sent to the study subjects. Study Doctor Stefan Branth scrutinized Swedish translation.

Diarrhea was defined as type 6 and 7.

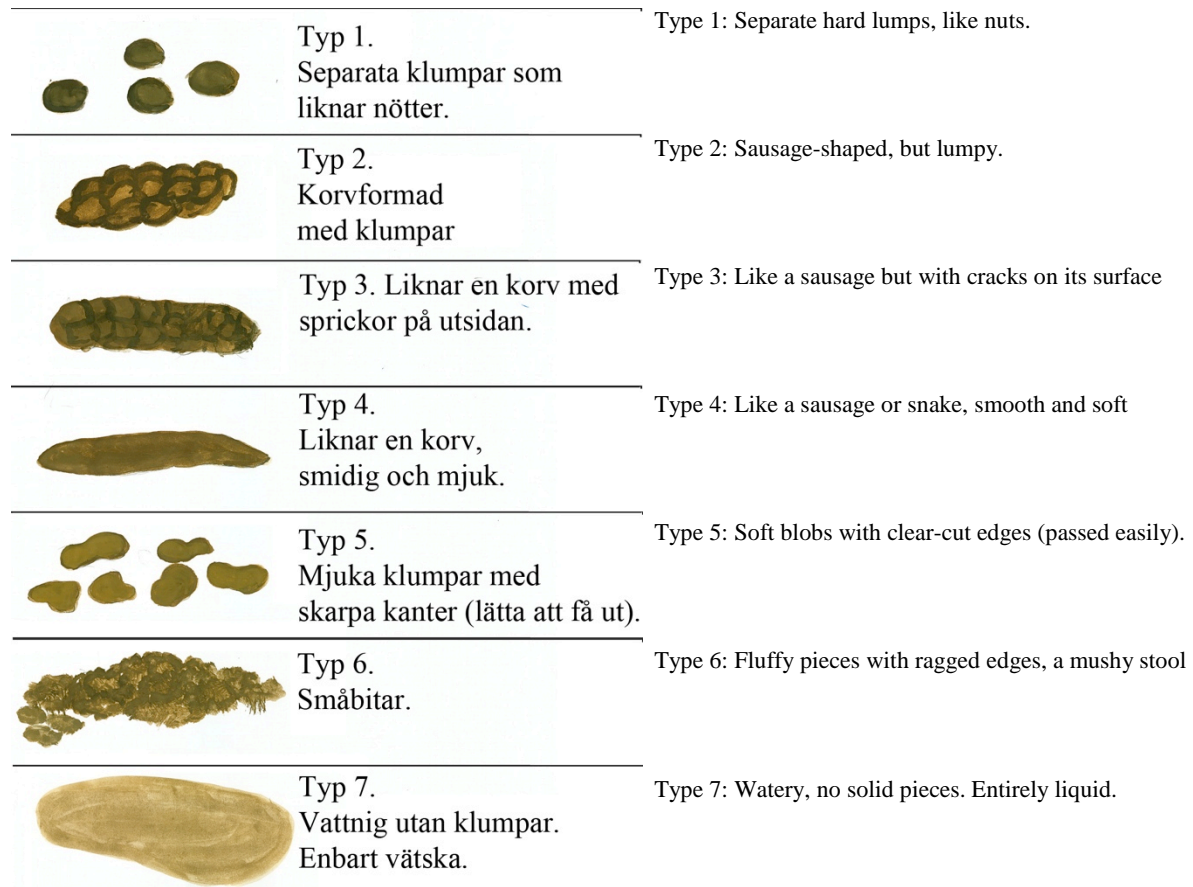


Figure 2. The Bristol Stool Form Chart with descriptions to the left and English descriptions on the right. Water painting by Elisabeth Köhlerstrand.

Study subjects classification of stool forms were sent in via an online form. Stool form charts were to be filled in by study subjects during five days; the three days with diet supplementation and two days thereafter. Data was collected for a total of five days to be able to track adverse effects of the treatments.

## 2.5 Study treatments

Study subjects included in the study were instructed to eat a supplementary diet according to the scheme in Table 5.

*Table 5. Study subjects were instructed to eat the study product on a total of 8 occasions. The weight of one sachet of egg yolk powder was 4 gram.*

Day 1	Day 2		Day 3 Stockholm Marathon		
Breakfast	4g	Breakfast	8g	Breakfast	24g
Lunch	4g	Lunch	8g	After finish	12g
Dinner	4g	Dinner	8g		

Each study subject was randomly assigned to either B 221 or placebo (standard spray-dried egg yolk powder) treatment. No restrictions were given except that study subjects were not allowed to eat SPC products.

Code lists were not available for persons directly involved in the study. B 221 and placebo were manufactured by Källbergs AB. B 221 and placebo were packed in identically looking sachets, each containing 4 g of product.

Taste and appearance of B 221 and placebo was equal. Different time stamps on the sachets could separate B 221 and placebo. Sachets containing placebo had been tested not to contain AF.

Lantmännen AS-Faktor AB conducted the packaging and distribution.

The study subjects received the study product by mail. No collection of unused product was carried out.

## 2.6 Statistics

Mean values of the prevalence of diarrhea were calculated. The difference between the two treatments was evaluated using Students t-test. The level of significance tested was 95%.

### 3 Results and Discussion

Table 6 shows that the active group had 29 study subjects filing their data on the first day of the study and that the group had one study subject dropping out during the study. The placebo group decreased from 28 to 25 reporting study subjects in the same time interval. In the placebo group 1 person dropped out of study on the day of the race and 2 more dropped out on the 4<sup>th</sup> day.

*Table 6. The number of study subjects that delivered their diaries on the different days of the study.*

Treatment	Day 1	Day 2	Day 3	Day 4	Day 5
			Stockholm Marathon		
Active	29	29	28	28	28
Placebo	28	28	27	25	25
Active + Placebo	57	57	55	53	53

Table 7 presents the prevalence of diarrhea in the two groups on the day of the race. On the day of the race 55 study subjects filed their answers. The active group consisted of 28 study subjects and 17 of them, 10 men and 7 women, experienced diarrhea. The placebo group consisted of 27 study subjects and 12 of them, 9 men and 3 women, experienced diarrhea. In percentage, 61% in the active group and 43% in the placebo group experienced diarrhea on the day of the race. The difference between the two treatments was not significant ( $p=0,23$ ). The low number of study subjects included in the study together with the large amount of drop-outs lead to an uneven distribution of male and female study subjects between the groups.

*Table 7. The number of male and female study subjects that experienced diarrhea on the day of the marathon race.*

Treatment	Male	Female	Total
B 221	10 (59% of the men)	7 (58% of the women)	17 (61% of the whole group)
Placebo	9 (41% of the men)	3 (50% of the women)	12 (43% of the whole group)

Study subjects that did not send in complete data for all five days were asked to clarify why they did so in a mail-based post study drop out survey. A total of 28 intended study subjects replied on the survey. Dropout reasons and the number of study subjects agreeing with respective reasons are presented in Table 8. Several dropouts were connected to sickness and injuries. Other dropouts were connected to the fact that the B221 is an unknown product and the study subjects did not want to jeopardize their performance. Too extensive work with data registration has also been reported as a dropout factor. Only 3 study subjects reported that their reason of dropout was that they had problems with ingestion of the egg-powder.

*Table 8. Seven different reasons for drop-out reported by the 28 intended study subjects that responded to a post study survey.*

Did not participate in the marathon	8
Injured	4
Sick	5
Did not get the study product in time	5
Was not able to drink/eat the egg powder	3
Did not want to risk the result of the marathon by testing, an in the context, untested product.	6
Too many questions to answer	6
Data registration problems	4

Study subjects were asked to report health issues during the five days of the study. The number of reported adverse events was 16 for the group receiving B 221 and 24 for the group that received placebo.



Further, which can be seen in Table 9, there was as difference in the number of reported adverse events in the two groups: the active group reported 16 adverse events during all 5 days of the study and the placebo group reported 24 adverse events for the same time.

*Table 9. Summary of reported adverse events in the two groups.*

Day 1-5	B 221	Placebo
Headache	11	6
Throat ache	1	3
Nausea	2	1
Cold	1	9
Dehydration	-	1
Cramp	-	2
Sore muscles	1	2
Total	16	24

Table 10 summarizes reported adverse events on 1<sup>st</sup> day of the study. A total of 12 adverse events were reported in 4 categories: headache, throat ache, nausea and cold. Active group reported 4 adverse events and the group given placebo reported 8.

*Table 10. Number of study subjects that received B 221 or placebo and of whom reported health problems during the first day of the study.*

Day 1	B 221	Placebo
Headache	2	4
Throat ache	1	1
Nausea	1	-
Cold	-	3
Dehydration	-	-
Cramp	-	-
Sore muscles	-	-

Table 11 summarizes reported adverse events on the 2<sup>nd</sup> day of the study. A total of 6 adverse events were reported in 2 categories: headache and cold.

*Table 11. Number of study subjects that received B 221 or placebo and of whom reported health problems during the second day of the study.*

Day 2	Active	Placebo
Headache	2	1
Throat ache	-	-
Nausea	-	-
Cold	-	3
Dehydration	-	-
Cramp	-	-
Sore muscles	-	-

Table 12 summarizes reported adverse events on the 3<sup>rd</sup> day of the study. A total of 5 adverse events were reported in 4 categories: headache, nausea, dehydration and cramp.

*Table 12. Number of study subjects that received B 221 or placebo and of whom reported health problems during the third day of the study.*

Day 3	Active	Placebo
Headache	2	-
Throat ache	-	-
Nausea	1	-
Cold	-	-
Dehydration	-	1
Cramp	-	1
Sore muscles	-	-

Table 13 summarizes reported adverse events on the 4<sup>th</sup> day of the study. A total of 9 adverse events were reported in 5 categories: headache, throat ache, nausea, cramp and sore muscles.

*Table 13. Number of study subjects that received B 221 or placebo and of whom reported health problems during the fourth day of the study.*

Day 4	Active	Placebo
Headache	4	-
Throat ache	-	1
Nausea	-	1
Cold	-	-
Dehydration	-	-
Cramp	-	1
Sore muscles	1	1

Table 14 summarizes reported adverse events on the 5<sup>th</sup> day of the study. A total of 8 adverse events were reported in 5 categories; headache, throat ache, nausea, cramp and sore muscles.

*Table 14. Number of study subjects that received B 221 or placebo and of whom reported health problems during the fifth day of the study.*

Day 5	Active	Placebo
Headache	1	1
Throat ache	-	1
Nausea	-	-
Cold	1	3
Dehydration	-	-
Cramp	-	-
Sore muscles	-	1

The main issue with the study was that it did not reach the planned number of study subjects entering and completing the study. The plan was to enroll 200 study subjects in the study, 100 subjects in each group. Out of the 169 runners that sent in their screening data 103 did actually meet the study criteria.

The study was performed at one single event only to create as similar conditions as possible in factors that possibly could have had an impact on the study subjects; weather, running course and stress (Ulgheri *et al.*, 2010). However, diet is a factor that was not controlled and this could have affected the outcome of the study (Rehrer & Janssen, 1989).

The study gives an indication that B 221, in the dose that was administrated in the study, does not diminish the prevalence of diarrhea among runners with a history of diarrhea in connection with long distance running. More information, meeting with the study doctor could possibly have diminished the amount of dropouts. A pilot study prior to the marathon could have given important experiences and data for the study design.

## 4 Conclusion

This study could not show support for the hypothesis that a treatment with egg yolk powder high in Antisecretory factor, AF, had a reducing effect on the prevalence of diarrhea among marathon runners. The prevalence of diarrhea was lower in the placebo group. However, the low number of study subjects does not allow for any conclusions.

No data on dose in healthy individuals was available when the study was designed. It is possible that the dose was too low. For future studies a key element would be to include a proper dose finding titration. Further, no severe side effects of the treatment were reported in either group, a finding that can be used in future design of studies with B221 and athletes.

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## Appendix 1 – Popular Scientific Summary

Gastrointestinal disturbances during and/or after running, commonly known as “runner’s trots”, are common among marathon runners. In previous studies about one third of the marathon runners reported that they had suffered from diarrhea in connection to marathon runs and about one third reported that they had a strong urge to defecate.

The cause of these disturbances has not yet been determined. The redirection of blood from the gut to the skeletal muscles is one factor that is believed to affect the function of the gastrointestinal system. Other commonly mentioned factors are stress, low blood sugar and ingestion of sweeter sport drinks.

In 1984 the scientists Stefan Lange and Ivar Lönnroth at the University of Gothenburg discovered a protein with anti-inflammatory and anti-secretory properties. The protein was later named Antisecretory Factor (AF). B221 is a spray-dried egg yolk powder with a high content of AF. This powder has in earlier studies successfully stopped acute and persisting diarrheas among young children and diarrhea as a result of chemo- and radiation therapy.

A number of 103 runners intending to participate in the 2011 Stockholm Marathon and who had an extensive history of diarrhea in connection to marathon running were selected for the study. The runners complemented their normal diet with B221 or common egg yolk powder (placebo) two days prior to and on the day of the race. The runners did not know if they had been given B221 or placebo. During these days and two days thereafter (a total of five days) the runners reported their stool consistency using a visual guidance complemented with explanations.



Unfortunately the study suffered from many dropouts. Many of the dropouts were connected to sickness and injuries. Other runners did not want to jeopardize the outcome of the race with an unknown product. Some reported that the egg powder had arrived to late or that there was too many questions to answer.

This study could not show support for the hypothesis that a treatment with egg yolk powder high in Antisecretory factor, AF, had a reducing effect on the prevalence of diarrhea among marathon runners. The number of runners that reported their stool consistency on the day of the race was 55. The group receiving the B221 had a slightly higher percentage of diarrheas on the day of the race than the placebo group. However, the difference between the two groups was not statistically significant. That is, there is a possibility that the outcome was due to chance.