



**Antisecretory proteins and Medical Food
– new options for an effective treatment
of inflammatory bowel disease**

**Summary of a Symposium,
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Protein AF: Synthesis and biological effects

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The Antisecretory Factor (AF) is an endogenously produced peptide that modulates or regulates the salt and water balance in different membranes of the body. We have demonstrated that the AF peptide in different experimental systems, mainly in rat, inhibits cholera induced secretion. The antisecretory peptide also affects other types of secretions produced by other types of bacteria. All tissues in e.g. pig produce AF, such as in the intestines, lung, nose, gall bladder and the balance organs of the ear. The Swedish Farmers Cooperative, Lantmännen, contacted us in 1986 when the use of antibiotics in pig feed was banned in Sweden. As a result, the prevalence of diarrhoeas increased. We therefore developed a feed for small pigs that would trigger the production of AF. This treatment proved to be effective and the decrease in diarrhoea was correlated to the AF-production. Even the mortality was lowered. Thanks to these positive results in animals we discussed with Stellan Björck, M.D., PhD, and Prof. Ingvar Bosaeus how we should organize the first studies in patients. In the following studies in patients with short intestines, we were able to see that the bowel movements were affected when the concentration of AF was increased. An increased AF was only achieved in patients with short intestines exceeding a length of one meter.

The Antisecretory Factor – the development of a model and initial studies

The Antisecretory Factor (AF) is an endogenously produced peptide that modulates or regulates the salt and water balance in different membranes of the body. It is a regulative system that I worked on during my time as a PhD candidate. At first we developed a model to measure the hypersecretion or the pathological secretion in the intestines. In this model the rat is opened, a 10–15 cm long segment of the small intestine is sectioned and a bacterial toxin is injected, in this case cholera toxin. The segment is put back into the abdomen, the rat is sutured and then we had to await the time required. Maximal secretion occurred after 60 minutes to 7 hours, depending on which toxin that has been used. It is difficult to choose another mode of measuring intestinal secretion, gut motility and different types of intestinal reactivity to bacterial toxins etc than conducting in vivo trials, often in non-sedated animals. In other words we have a dose-response, where we have a reactivity in the small intestine depending on the amount of the secretion releasing agent in question that we have been using.

In our studies we have been using cholera toxin. Using this toxin means that the intestinal integrity is unaffected, nothing affecting the morphology. There

is only a pathological salt-water balance that can cause a loss of very large quantities of salt and water during a short period of time. There has been a case report of a patient who weighed 84 kg. He had, during a 24 hour period, registered a loss of 46 litres due to

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a cholera attack during his service in Vietnam. Consequently there is a very fast and dynamical flux change that occurs in these membranes when they are affected pathologically.

These results simply shows that the more toxin we use, the more water we have in the loops. A shift of the curve to the right shows less receptivity to the disease in question. The experienced clinician would say that this is nothing new. Specialists in infectious diseases and gastroenterologists know, for some 4000

years, that those who survive cholera or some other violent diarrhoeal infection are resistant 2–4 years afterwards. These people were forced to take care of sick or dead people since it was known that they would not get infected again. For the experimentalist, however, the above mentioned results imply several new aspects since we can now start to show interest in examining these resistance inducing mechanisms in the body, in this case in rat, and later on in pig.

In order to approach this problem we used a proven form of biological system. We immunised a large group of rats who were totally immune to cholera and transferred different types of extract from the im-

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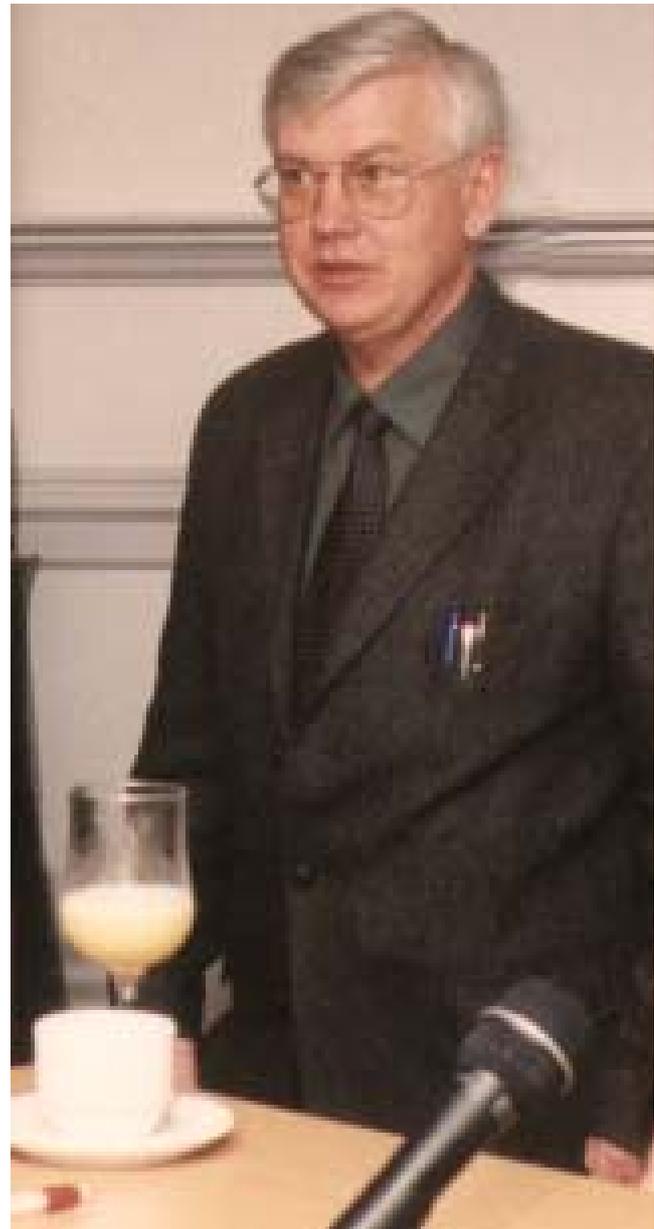
munised group to a virginal group that was very sensitive to cholera. We could then see which extracts that could influence the reactivity in the virginal rats, in other words a transfer from one system, insensitive, to a sensitive one; a very simple type of biology.

My collaborator, Ivar Lönnroth, M.D., PhD, did all chemical preparations of the tissues. We transferred almost everything, from cells to different tissues, from the muscles to the CNS. We came to the conclusion that the pituitary gland is a good tissue to work with since it contains a large dose of what we wanted to research, namely a substance that is capable of bringing about an antisecretory or an inhibitory reactivity in the receptor animal.

We extracted a number of pituitary glands and separated the mixture after molecular weight. Then we selected the different fractions in order to test them in the receptor animal. The whole reactivity was collected in a span of approximately 60 kilodalton, as we knew that it was a protein and was to be found within this span. We refined the system and eventually discovered that it was a peptide. We sequenced it and sent these sequences to Gene Bank. To our great joy, they affirmed that what we had discovered was a totally new peptide that had not been described before.

A totally new peptide

Hereafter we showed that the peptide, in different experimental systems, especially in rat, affected the cholera toxin and inhibited secretion. It affected the Campylobacter toxin and Clostridium difficile toxin A,



derived from two bacteria, and Okada acid, which is the toxin from sea mussels that is very effective in causing diarrhoea. It could, in other words, most certainly affect a very general system triggering secretion. The reason for testing all these toxins is that they provoke secretion biologically in totally different ways and which have not yet been described in detail. The antisecretory peptide however, affected all types of secretions. It affects something basic and phylogenetically very old in the cell, namely a patho-physiological mechanism which probably comes before some cyclic nucleotides, before all types of chemical reactivity in the cell that have been described to this date as regards diarrhoea.

We were also able to split around 90% of the peptide and retain a small active fragment of 8–20

amino acids that still functions as an antisecretory unit. It is possible to perform this with almost any peptide that is biologically regulative in mammals. It also follows different types of reactivity for peptides, we have a bell-shaped curve, we can get a maximum and a window in which the concentration operates.

The ban on antibiotics – negative and positive consequences

Now back to reality. We were contacted by The Swedish Farmers Supply and Crop Marketing Cooperative, Lantmännen, in the beginning of 1986 as the use of antibiotics was prohibited in pig feed. The diarrhoeas in the pig population started to increase. The production units are large and modern and closely monitored by skilled “biologists”. If an infection occurs in this system, large economical values are at stake. The concentration of mammals is dense from a biological point of view. We co-operated with Kjell Martinsson, professor in pig health, and Leif Göransson,

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son, Doctor of agriculture, at the Lantmännen Pig Research Farm, Sveriges SvinCenter, in Svalöv. The only thing we knew about pigs at that point was that Ivar Lönnroth and I together with Erik Skadhauge at Fredriksberg’s College of Agriculture had done exactly the same as in rats, namely a dose-response study with AF in pigs. Hence, we knew that they were sensitive to Antisecretory Factor and that it was produced endogenously. Looking back historically, how diarrhoeic diseases have been treated, we also knew that sugar and amino acids had been used. That is all. In cases of very severe hypersecretion, a mild or very sedating membrane stabilizing substance; ethanol or opiates, was added depending on the culture. I therefore tried the sugar alcohol sorbitol on the rat. I immunized the rat orally, provoked a secretion with 5,5% sorbitol and it proved much more efficient than cholera toxin in inducing a production of Antisecretory Factor. Together with especially Leif Göransson we produced a pig feed where we had manipulated the amounts of sugar and amino acids to obtain an optimal concentration of Antisecretory Factor. The pigs responded effectively to this feed and in the initial trials we could see that the post weaning diarrhoea, PWD, decreased quickly from 50–60% to

10–20%. This reduction in diarrhoea was correlated to the AF-production, i.e. the AF-levels were significantly higher in treated animals. We are now able to say that the problem with diarrhoea in the pig population has improved.

We could also note a growth increase, a daily weight gain, which is encouraging as we are now starting studies in children. If the pigs have healthy intestines due to a high production of AF they will gain weight significantly more than the controls who have a clinical or sub-clinical diarrhoea. In some children we have also seen this; not in a double-blind, controlled study, but in anecdotal cases we have noted this when the diarrhoeas have been reduced. The growth increase in these children with a reduced flow can be changed in a short time. Marie Krantz, M.D., PhD, at the Sahlgrenska Hospital and Prof. Yigael Finkel at the Karolinska Hospital are in charge of these paediatric investigations.

Also the mortality in the pig population was reduced due to their improved intestinal health. All tissues in pigs produce AF. With immunohistochemistry we can show that it is found in the intestines, in lymphocyte cells that morphologists are in the process of mapping. It is also located in the lung, shown using both in situ hybridisation and immunohistochemistry. AF is also found in the pig’s nose, gall bladder and the balance organs of the ear.

The first studies in patients

Thanks to the positive results in pigs, we discussed with Stellan Björck, M.D., PhD, and Prof. Ingvar Bosaeus how we should organize the first study in patients. We were our own first patients. We received pig feed from Svalöv from which we baked rolls and made muesli. The manufacturing process is complicated. After having eaten the pig feed for up to four weeks, middle-aged doctors, PhD candidates and other co-workers all had a significant and sustainable increase in AF. Thereafter Ingvar Bosaeus wanted to test this on patients with short intestines, this being his speciality, and as these patients normally have high secretions. The first attempts showed no correlation whatsoever. But when we analysed the system more in detail we got a correlation in some patients. The bowel movements decreased when the AF-concentration increased as a result of the treatment with these cereals. We could not understand this fully since we also had some nonsense results. We discussed with Stellan and Ingvar how to interpret this. The length of the intestines probably have to exceed approximately 1 meter, which possibly is correlated to a certain ability to respond to the cereals with a resulting increase in AF and a reduced secretion. We are now continuing the measurements on Prof. Bosaeus’s patients.

Specially processed cereals – a treatment alternative for certain surgical patients

Stellan Björck, M.D., PhD, The Surgical Department, Sahlgrenska University Hospital, Mölndal, Sweden

We have conducted a randomised double-blind study in patients with ulcerative colitis and Crohn's disease. In the treatment group who received the specially processed cereals (SPC) as a supplement to their ordinary food, the amount of AF in plasma is drastically increased, and the increased levels are sustained, whereas nothing happens in the placebo group. The patients recorded their intestinal function in a diary and patients on the SPC treatment had a significantly better intestinal function. Intestinal biopsies also show that these patients will have a pronounced accumulation of AF in the epithelial cells of the intestines. These positive results have implied that we now initiate the treatment with AF to more patients who undergo operation in the alimentary canal and where we know by experience that the result will lead to an insufficient intestinal function. We start the treatment very early, sometimes already the first day, by giving eggs with a high concentration of Antisecretory Factor, AF (Salovum) dissolved in ordinary juice. This is a way of giving very high amounts of AF directly to the intestines without having the body producing it first. Most of the time we can then stop giving the egg powder and change to a maintenance dose of cereals. We believe the mode of action to be that the net absorption is increased by inhibition of the secretion. Moreover, there is no doubt that AF has very pronounced anti-inflammatory effects.

Positive results in ulcerative colitis and Crohn's disease

The first study that we performed was mainly in patients with ulcerative colitis but also with Crohn's disease. They all had an insufficient intestinal function and consequently visited the bathroom often. They were however not in a difficult, active phase of their disease, but they had a chronic insufficient intestinal function. We randomised patients to a specially processed diet or a placebo diet that they were instructed to eat every day during 1 month. The logistics worked very well and patients were eager to enroll in the study. 26 patients were given the specially processed diet and 24 patients received the placebo diet. Normally people have no measureable levels of AF, but upon receiving a specially processed diet like this in addition to regular food, the level of AF in plasma increases drastically, whereas nothing happens in the placebo group. Two months later these levels are still sustained in the AF-treated patients (figure 1). The patients kept diaries of their intestinal function and also stated their final result. The im-

provement in intestinal function is clearly significant in the group who had received the specially processed diet and who furthermore had high AF-levels in their blood. We also observed a large number of other factors, e.g. rectal biopsies. Among them, the only

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significant change was found in the group with the most pronounced inflammatory changes of the mucosa. In this group as in the active group we had significant changes as regards the histology. We looked at various blood factors, such as CRP, cholesterol, triglycerides, HDL-cholesterol, but no significant changes were seen. After eating this diet

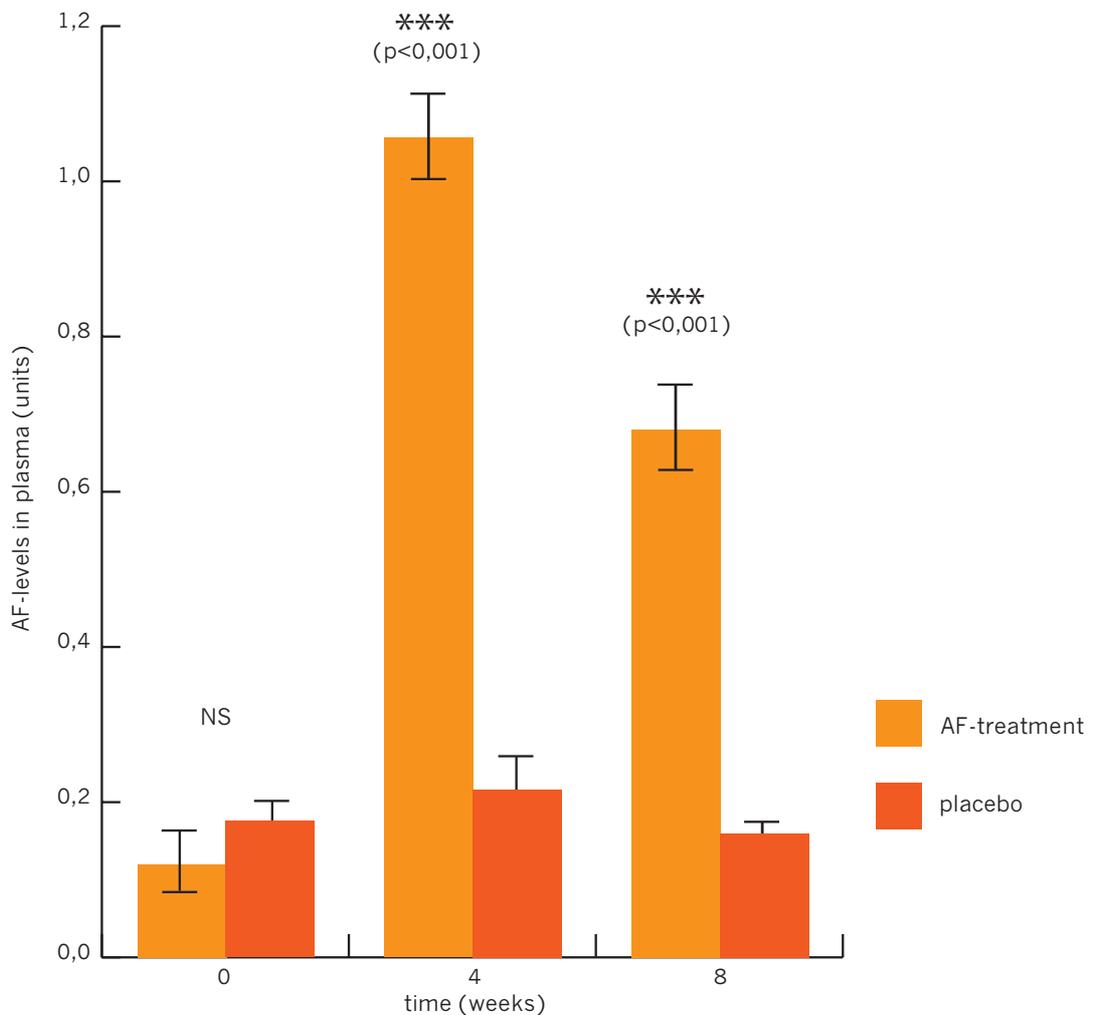


Figure 1. Patients treated with specially processed cereals (SPC) had significantly higher AF-levels in plasma than the placebo group. SPC-treated patients also had a significantly better intestinal function.

a drastic accumulation of AF is cytoplasmatically dissolved in the epithelial cells of the intestine. When looking at biopsies, it is clearly visible for the eye that something has happened from the start until the end of the trial.

Different prerequisites in different parts of the intestine

What are the prerequisites when we have to deal with patients whose intestines have been removed for one

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reason or another. If we start with the jejunum we know that it absorbs nearly all fat, carbohydrates and proteins from a meal. The proximal jejunum also absorbs iron, calcium and magnesium. The ileum has

the same pattern of absorption as the jejunum, why the jejunum can be removed and its function can be taken over by the ileum. In the ileum there are two specific transport systems, partly for the biliary salts and partly for B12. The ileum also has a considerably higher adaptive ability than jejunum, so if one should be affected by something it should preferably be in the jejunal tract. In the ileocaecal region we know that it works as a unit regulating the gastric emptying and transit through the small intestine. We have also an important brake mechanism in the distal ileum which is called the ileal brake. When we are forced to remove the ileocaecal region we know that we accelerate gastric emptying, see a faster passage through the small intestine and get a proliferation of colon bacteria in the distal ileum. The colon is most important for the water absorption and the electrolytic absorption and the colon has a large extra and reserve capacity for absorption. It has been shown experimentally that the right part of the colon, caecum, is able to absorb up to 5 litres of liquid daily.

After a partial ileocolic resection, the diarrhoeal volume is dependant on how much of the colon that has been removed and not so much of the ileal length.

If we remove the colon, approximately 100 cm of jejunoleum is required not to develop a short bowel syndrome. In order to trigger AF-production in the body approximately one metre of small intestine is required.

Every time we have to remove parts of the intestine the intestinal adaptation takes place. This is a process that takes a certain number of months. Normally it takes three months to restore most of the function. This happens through extension and dilation of the remaining intestinal part. The villus height is also increased in the mucosa and with this the number of enterocytes, who will be high and cylindrical,

“We believe the mode of action to be a net absorption increased by inhibition of the secretion.”

is also elevated. It is necessary to have food in the gut endothelium to trigger the system, and that the gall, pancreatic juice and also gastrointestinal hormones are present.

Treatment suggestion and mode of action

My colleagues and I at Sahlgrenska Hospital/Möln-dal have now initiated treatment with AF to all patients undergoing operation in the alimentary canal and where we know by experience that the result will be an insufficient intestinal function. We start the treatment very early, sometimes already the first day, by giving eggs with a high concentration of Anti-secretory Factor, AF (Salovum) dissolved in ordinary juice, given orally or by probe. The mechanism is that if you give specially processed cereals to hens, they will lay eggs whose yolk contains very high amounts of AF. This will then be a way of giving AF directly to the intestines without having the body producing it first. However, we want the patient's body to start an endogenous AF-production as soon as possible and we initiate that by giving the patients the specially processed cereals orally. It takes about 10 days until we have maximal AF-levels with a stimulation of the endogenous production. Most often we can then stop giving the egg powder and change to a maintenance dose of cereals.

We believe the mode of action to be a net absorption increased by inhibition of the secretion. We know that there must be a balance between them. When there is a loss of less than one metre of distal small intestine we know that the patients are affected by secretion in the colon caused by biliary salts. It is probable that we inhibit that secretion with the high level of AF. When there is a loss of more than one



metre this will result in fatty acids in the colon that will start its own secretion. We believe that AF also has an inhibitory effect on this. Moreover, there is no doubt that AF has very pronounced anti-inflammatory effects.

Question: The MagiForm product range is recommended to more or less all patients suffering from gastroenterological problems. What happens to those not having an increased secretion?

Answer: The individual who has a normal intestinal function can nearly have a feeling of constipation if he or she eats the amount of cereals that we recommend in order to trigger the system maximally. The IBS patients have a very much disturbed motility as a cause and my experience is that many of them may worsen, the abdomen hurt more, they experience more flatulence. The patients suitable for this treatment are those who have diarrhoea. IBS with diarrhoea is an ideal patient.



Antisecretory proteins – a new therapy in IBD

Stefan Lange, M.D., PhD, The Institute of Clinical Bacteriology, University of Gothenburg, Sweden

Our double-blind study with eggs with a high concentration of Antisecretory Factor, AF (Salovum) in patients with severe relapses of ulcerative colitis shows that we had an effect mainly on the inflammatory parameters compared to the patients that were given the placebo egg powder. These differences are now being investigated.

Ulcerative colitis

I will present the result from Anders Eriksson's, M.D., PhD, and our study on the AF egg powder (Salovum) in patients with ulcerative colitis with severe relapses. The patients are on total parenteral nutrition, TPN. 22 patients participated in this study, 10 of them received eggs with a high concentration of AF, 12 patients were given a placebo egg powder.

More on the mode of action

Considering to the mode of action, we discussed which set of patients to choose. We evaluated that AF egg powder (Salovum) had a dramatic effect in Crohn's disease. We are now conducting very direct investigations on the peptide mechanism on different cellular and reactivity patterns in vitro and we intend to transpose them to in vivo. We can say that we have good trial assays to shed light upon the enteric nervous system, the brain-gut axis. We know that it affects the ion channels and has an anti-inflam-

matory effect. We are now focusing on which type of inhibition that it has and if it affects the vascular permeability.

The result of our double-blind study on ulcerative colitis came surprisingly late as regards the effect on the disease. We are now investigating the differences

"We are now conducting very direct investigations on the peptide mechanism. We know that it affects the ion channels and has an anti-inflammatory effect."

between the treatment groups, i.e. in the patients who received the egg powder with a high concentration of AF compared to the patients on the placebo egg powder.

Treatment with specially processed cereals (SPC) in severe Mb Crohn

Morteza Shafazand, M.D., Department of Medicine, the Section of Gastroenterology, Sahlgrenska University Hospital/Östra Hospital, Sweden

We had tried all treatment possible, including infliximab, cortison, 5-ASA and TPN, in a patient with a 20-year past history of a severe Morbus Crohn. He got worse and relapsed with up to 15 bloodstained diarrhoeas daily and he experienced fever and stomach pain. His state deteriorated. Only surgery remained as a last alternative, but he refused, as he did not want to lose more intestine. He kept asking us if there was something else he could try, so we told him about Antisecretory Factor and he definitely wanted to try it. We initiated the treatment with eggs with a high concentration of Antisecretory Factor, AF (Salovum), which resulted in a reduction of his diarrhoea already after two days. After 12 days he had no diarrhoea at all. His fever disappeared, as well as the abdominal pain, and he felt a lot better. We noted an effect on the laboratory parameters and the inflammatory parameters were improved as well. We removed the TPN and he could be discharged with a total length of hospital stay of three weeks. Bearing in mind his severe condition and all other facts, including the failure of conventional treatment, we believe that it is AF that has had effect in his case and that it is an effective additional treatment.

Treatment with Salovum and SPC in severe Crohn's disease

I will tell you about a case report of a patient suffering from Crohn's disease where we have used this new treatment alternative. The case is about a 38-year old man with a 20-year past history of severe Morbus Crohn. He underwent two surgical operations, 1984 and 1986, with resection of parts of the colon, and about 60 cm of his large intestine remained. In 1988 his distal ileum was affected and he was operated. He had also been having problems with perianal fistulas. His disease had clearly progressed the last year before we initiated this treatment. He had an activity more or less all the time and we had to give him quite high doses of cortisone. He lost 25% of his habitual weight. Unfortunately he did not tolerate immunosuppressive treatment with Imurel and Puri-nethol. He experienced side effects from the pancreas and the liver, and general arthralgia. When we suggested alternative immunosuppressive treatment he declined since he and his wife had a strong desire to become parents. The treatment with immunomodulation, infliximab, gave no positive results on his intestine. His state worsened, he got a relapse with up to 15 bloodstained diarrhoeas daily, and he experienced fever and stomach pains. We

quickly arranged a colonoscopy which was extremely painful for him. The remaining part of the colon's tissue was heavily inflamed, almost necrotic. We could not even get through with the anastomosis, being so narrow due to the swelling. Having a close collabor-

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ation with the colorectal surgeons at the Östra Hospital, we called on Dr Öresland. He saw no other way than removing the colon followed by a permanent stoma in his stomach. We initiated the treatment in the conventional way. The patient received high doses of cortisone rectally, 5-ASA, total parenteral nutrition, antibiotics, with the result that he only deteriorated. Only surgery remained as an alternative but the patient did not want to lose more of the colon. He kept asking us if there was nothing else to be done. At this



stage we informed him about the AF and he insisted on testing it.

We have already stated that AF most certainly affects the secretion and inflammation in a positive way. It has also resulted in a clinical improvement. Today AF exists in two forms, a spray dried egg powder, Salovum, that can be administered in a passive way or by stimulation of the patient's endogenous production of AF with specially processed cereals (SPC). We started giving the patient the powder form, with an overlapping treatment from day 5 when we gave him specially processed cereals. The only reason for giving him fine pressed cereals at first was that we were afraid that ordinary SPC would get stuck in his anastomosis. From day 8 he received regular specially processed cereals. Up to this day he is on this diet. At an early stage, already after 48 hours, we noted a reduction in diarrhoeas. After 12 days they had stopped completely. He had loose defaecation a couple of times but no blood. His fever and

abdominal pain disappeared and he felt much better. We saw the effect on the laboratory parameters and the inflammatory parameters improved as well. We removed the TPN and he could be discharged after three weeks length of hospital stay.

Figure 2 illustrates the effect of this treatment on his frequencies of diarrhoeas during different weeks; a fast reduction of his intestinal secretion and a sustained effect the remaining weeks.

On a VAS scale the patient registered how he felt about his intestinal function and general condition and we could see a clear improvement. Three months after initiation of the treatment he had regained his 25% weight reduction and was back to his normal weight. He had personally stopped to take all the medication that he had received over the years. We

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performed a colonoscopy on him and this time there was no pain involved and it was the same colonoscopist who performed the procedure. There was no problem to get through the anastomosis and the small intestine looked fine. The colon was almost totally recovered, there was a slight tendency of oedema and a slight redness. Even the CDAI was lower, 150 compared to over 600 when he was admitted.

What remains today is that the patient still suffers from intermittent fever tops and arthralgia of unknown nature. We have taken systemic samples but have not found anything. He has been referred to a rheumatologist. He also has intermittent abdominal pain but we can not with certainty relate this to his intestine. The colonoscopy revealed that no obstruction existed, nothing that could explain his discomfort.

AF-powder and specially processed cereals is an effective additional treatment

Which conclusion can be drawn from the actual case? Bearing in mind his severe condition, the progression the last year and the acute relapse on top of this, where all customary treatment failed, followed by the rapid effect of the AF powder and the specially processed cereals which reversed his severe medical state, we can not interpret it in any other way than that AF has had effect in his case. Most certainly AF is an effective additional treatment.

We believe that it is wise to try this new treatment

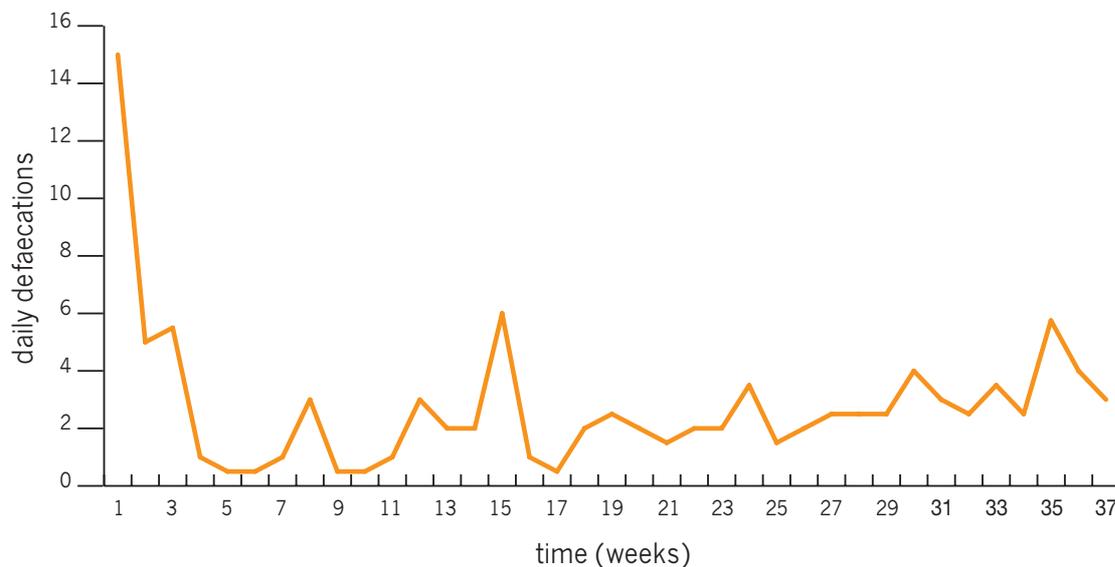


Figure 2. Initiation of treatment with Salovum and SPC dramatically decreased the diarrhoeic frequency from day 2. After 12 days the diarrhoeas had stopped completely and the good effect has been sustained.

on patients who, in one way or another, are refractory to customary treatment.

Question from the chairman: Can it be that the bacterial flora is changed in some way so there is a secondary effect not related to Antisecretory Factor?

Answer: No, we do not believe that. I can tell you that we had a couple of identical cases at the Östra Hospital with the same clinical symptoms and where ordinary treatment failed. We treated them with the same AF products and they are feeling very well.

Question from the chairman: When hearing these patient case stories one nearly gets the feeling that the anti-inflammatory effect is primary and the reduced secretion is secondary. But looking at the Factor per se one believes that antisecretion is primary.

Answer: There is obviously an effect on both parameters. His intestinal secretion was heavily reduced and we also noted an effect on the laboratory parameters and the inflammation, but which of them being most important is difficult to say with certainty. We know that it affects both parameters.

Question from the chairman: Have you tried to remove these specially processed cereals from this patient? Have you not dared to do it?

Answer: The patient declined. He does not want us to remove the AF products. The same applies for the other patients. On the other hand, he receives no other medication.

Question: The two other cases at the Östra Hospital that you were talking about, do you continue with the immunosuppressive treatment?

Answer: Yes, but one of them has stopped all his medication as far as I know.

“The rapid effect of the AF powder and the specially processed cereals which reversed his severe medical state, we can not interpret it in any other way than that AF has had effect in this patient’s case. Most certainly AF is an effective additional treatment.”

Question: When you initiate AF treatment, do you continue with ordinary treatment and add this?

Answer: In this dramatic case the patient received ordinary intensive treatment and then we added the AF products. It was the same in the other two cases. But it is noteworthy that we started with ordinary treatment, but without effect.

Question from the chairman: We now hope that you will continue with controlled randomised clinical studies.

Answer: In addition to the already conducted studies, more studies will be initiated.

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**Treatment with specially processed cereals (SPC)
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