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* This English Edition is a translation of the newsletter published in Japanese on April 24, 2009

Cover photograph

The 1st Symposium of AHCC Research Association (June, 1995)
Gastrointestinal diseases are one of the most common ailments in clinical practice throughout the world. So common in fact that it is actually ‘normal’ for any patient to have gastrointestinal symptoms every now and then. Fortunately most of these are not severe or life threatening: bloating, diarrhoea, constipation, pain, discomfort, and so forth. Acute and chronic diarrhoea affect people of all ages and conditions all over the world, but specifically it endangers the lives of millions in underdeveloped countries. Acute diarrhoea is typically infectious in origin and of self-limiting character, and normally it poses no threat to the patient provided good (re)hydration is maintained and that the general condition of the patient is not critical. On the other hand, many patients experience diarrhoeal episodes associated to trips (traveller’s diarrhoea) or chronic diarrhoea secondary to a variety of causes, which disrupt the normal functioning of the patient and his/her quality of life. At the other end of the spectrum, constipation is also commonplace, particularly in developed countries, and it tends to be chronic and related to lifestyle, particularly stress, sedentarism and low fibre diets. Diarrhoea and/or constipation can become chronic and associate with other symptoms such as bloating, a feeling of discomfort, etc., in a condition called irritable bowel syndrome (IBS). IBS is considered to affect some 15% of people but it is greatly underdiagnosed because 3 out of 4 affected persons do not seek medical advice. The exact cause of IBS is unclear, as is the case with all functional disorders, including fibromyalgia, non-cardiac chest pain, irritable bladder syndrome, dyspepsia, etc. Clearly, there is a psychological component to IBS. It appears however that about half of the IBS cases may be related to subclinical inflammation of the intestinal mucosa, giving rise to an exacerbated sensitivity of the enteric nervous system to mechanical distension of the colonic wall. It should be noted that overt inflammation is never found in IBS. Chronic inflammation is however the hallmark of Crohn’s disease and ulcerative colitis, jointly referred to as inflammatory bowel disease (IBD). These are characterized by chronic and relapsing inflammation of the intestine which is associated with diarrhoea, malaise, malnutrition and overall deterioration of the patient’s quality of life. However, there are important differences regarding regional distribution, type of inflammatory response and histological involvement. The pharmacological treatment is largely empirical, i.e. directed unspecifically at the inflammatory response, since the causative factors have not yet been identified and appear to be multifactorial. In addition, IBD patients often require surgery for adequate management of their disease.

Management of all these conditions is often tricky. One of the alternatives are prebiotics and probiotics. The rational basis for the use of these agents is the concept that alterations in the normal, host friendly intestinal flora is an underlying factor in their pathology. For instance, diarrhoea is often the result of disturbances in the host-flora delicate balance, as happens usually with antibiotic therapy and infection. Constipation may be the consequence of low bacterial
mass and increased transit time, thus allowing the colonic mucosa to absorb more water than necessary and producing difficult stool passage. IBS patients have documented changes in their intestinal flora, which may therefore be involved in the development of this condition. On the other hand, the role of the intestinal flora is of paramount importance in IBD, to the extent that in animal models inflammation cannot be elicited in its absence.

Probiotics and prebiotics are different tools originally geared to the same purpose. Probiotics are living bacteria which are administered to the host, acting by directly modifying the flora toward a favourable profile. Prebiotics on the contrary are nonabsorbable sugars that reach the colon intact and that are metabolic substrates for intestinal bacteria, in such a way that the growth of host-friendly species is selectively promoted (Lactobacillus, Bifidobacterium, etc.), thus tending to restore the lost equilibrium. Furthermore, prebiotics enhance the production of butyrate (as a byproduct), which is the main metabolic substrate for the colonic epithelium and has well documented antiinflammatory properties. In addition, our research group and other authors have characterized a number of actions of nonabsorbable sugars/prebiotics which are independent of their role as modifiers of flora. These include the inhibition of bacterial adhesion to the mucosal surface by acting as soluble decoy receptors or by blocking adhesion directly; changes in epithelial proliferation and differentiation; the modulation of the inflammatory response, altering cytokine production and leukocyte-endothelial interaction (12 : 99 : 116); and actions on intestinal permeability and transport.

Active Hexose Correlated Compound (AHCC) is a natural product obtained from a mixture of Basidiomyocyte mushrooms which is used as a human nutritional supplement and displays a variety of biological effects, including anticancer effects both in animal models and in clinical trials, prevention of the onset of diabetes induced by streptozotocin in animal models, prevention of liver injury produced by C1:C in mice or improvement of the immune response. These effects are ascribed in part to the immunomodulatory and antioxidant properties of AHCC. It is important to note that the main constituent of AHCC are oligosaccharides (~74%, ~20% being of the α-1,4-glucan type), the remainder being amino acids, lipids and minerals. The acetylated forms of the α-1,4-glucan type of oligosaccharides have low molecular mass (5kDa) and are considered the main active ingredient of AHCC. On the basis of these properties we hypothesized that AHCC might behave as a prebiotic and therefore exert antiinflammatory effects in vivo. Indeed this proved to be the case. Thus administering 500mg/kg of AHCC to rats with experimental colonic inflammation induced by the hapten trinitrobenzenesulfonic acid resulted in substantial amelioration of colitis, which was associated with changes in flora that are consistent with the mode of action of prebiotics. The immediate conclusion is of course that AHCC may be useful for the treatment of IBD in humans, but in parallel with the role of ‘pure’ prebiotics such as fructooligosaccharides, inulin or insoluble fiber, our results additionally suggest that AHCC may be appropriate also for such conditions as diarrhoea, constipation or IBS.

However, AHCC appears to be more than a prebiotic, exerting immunomodulatory actions that include a potentiation of NK cell activity, an enhancement of the lymphocyte response to mitogens and an increase of the activation of peritoneal macrophages. Because the molecular mechanism of AHCC responsible for the above mentioned effects is unknown, they may stem from the oligosaccharide components or from some other unidentified compound. Clearly, more research is needed to support the use of the fungi extract in intestinal diseases, but current data offer solid promise for an alliance between these friendly fungi and gut sufferers.
 Contribution  Nutrition is an essence of medical care

Teruyoshi Amagai
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[keywords]  
Medical care, nutrition, nutrient with positive effects, nutrient with negative effects, fractal theory, stochastic.

Proposition  
“Nutrition is the essence of medical care.”

There are at least 2 things that need to be clarified to judge the validity of this proposition, i.e. the definitions of the 2 terms: “medical care” and “nutrition.”

What is medical care?

Let us consider the meaning of “medical care.”

The only truth in the world that applies to all living organisms born on planet Earth, including humans: “All living organisms will die eventually.” Then, how do they die?

Courses of dying—even if we look at humans only, there should be as numerous ways of dying as the number of people born on the planet. With a bit of pondering, they may be classified under three categories.

1) Natural life span, 2) Accident, and 3) Disease.

The last among the above three, disease, occurs in many different types.

Firstly, cancer. There are many types such as cancers of esophagus, stomach, colon, lung, liver, biliary tract, pancreas, kidney, ureter, urinary bladder, ovary, cervix, uterine body, penis, and testis. There are many others and must be as many as the number of organs and tissues.

Next are the diseases other than cancer, for example, cerebrovascular accidents, myocardial infarction, hepatitis, hepatic cirrhosis, alcoholic hepatitis, non-alcoholic steato-hepatitis (NASH, currently a subject attracting intense attention), glomerulonephritis, and notably, chronic kidney disease (CKD).

If we compare today and ancient times, the number and courses of these human diseases are different. Over time, the total number of human diseases will continue to increase almost exponentially, being affected by innumerable factors such as social or economic backgrounds, developments in medicine, international exchange, and flight routes of migrating birds.

The whole picture of these increasing diseases is highly likely to be inferred by the picture of one disease (Ref to Note 1 "fractal theory.”)

Curing the morbid state of a patient you are seeing is clinically significant in saving the patient’s precious life and dignity, which is surely a noble action, but apparently a personal one.

Considering the fractal theory, however, medical practice to save the life of a particular patient is connected to all human beings. Actually medical care is the action with a broad perspective for determining or leading the future of the human race.

What is nutrition?

The meaning of nutrition. There are at least 4 significant functions of nutrition, as indicated below:

1) To construct the body.  2) To maintain the body.  3) To heal the body.  4) To destroy the body.

Living organism as a non-closed system

An organism can be considered as a closed system separated from the outer environment. But is it really a closed system? If we think even for a moment, the answer is “No.” Food, i.e. nutrition is ingested from the mouth, processed by chemical reactions (digestion) in the mouth, stomach, duodenum, jejunum, and ileum, and absorbed into intestinal mucosal cells to “construct the body” through metabolism.

In addition, energy is needed for all behaviors in the ever-changing daily life, such as body movements, consideration and judgment, etc. The energy is produced and provided through metabolism of 3 major nutrients, carbohydrate, fat and protein, to “maintain the body.”

Nutrition is also significant for “healing the body” in case of disturbance of homeostasis by diseases, using
Nutrition is an essence of medical care

However, not all the nutrients are beneficial to the body. If you do not selectively take the appropriate quality and amounts of nutrients, the nutrients will bear the 4th function with negative effects to destroy the body, in contrast to the first 3 significant functions mentioned above (as “positive effects of nutrients”).

Answer to the proposition

From the above-mentioned discussion, the answer to the question of "whether nutrition is the essence of medical care” becomes obvious. As for the morbid conditions in which homeostasis is disturbed by diseases, I personally feel that bacterial or viral infections account for about 80%, underlying almost all causes of death such as cancer, cerebrovascular accident, and myocardial infarction.

Nutrition is an action that affects infections underlying death and supports the body “resistance.” Nutrients are provided during this action.

Therefore, nutrition is the essence of medical care and the answer to the proposition is “Yes.”

AHCC and Oligonol to “heal the body” for homeostasis-prospects of “clinical nutrition for outpatients”

AHCC and an antioxidant, Oligonol are absolutely certain components of clinical nutrition.

I work at Fukushima Rosai Hospital once or twice per month on Mondays from 11:00 to 17:00 hours. My work is to provide nutritional intervention for patients with alimentary problems. I started developing a new system of comprehensive medical care for outpatients to resolve alimentary problems 6 months ago, with the cooperation of patients, senior nutritionists, nurses, pharmacists, radiologists, medical administration staff, social workers, and many other professionals of different departments at the hospital.

In my next article, I wish to write my personal opinion about our activities and future plans in relation to the application of AHCC and Oligonol in clinical nutrition for outpatients.

Note 1: It is said that there are two types in geometry. One is classical Euclidean geometry and the other is modern non-Euclidean geometry. I found the table that compared these two types of geometry under the scope of pharmacodynamics, a study to investigate changes in blood drug concentrations over time (Table 1). According to the table, when we try to visualize pharmacodynamics two-dimensionally to observe the changes in the blood concentrations over time of a drug, food-derived glucose (blood sugar), amino acid as a unit of protein, or fatty acid as a unit of fat, we express time along the horizontal axis and the blood concentration of drugs, nutrients, or antioxidants along the vertical axis. Then we look at the blood concentration in a huge two-dimensional plane. The two-dimensional distribution has a non-Euclidean relationship (Table 1).

(1) Non-Euclidean geometry is also expressed as fractal. Fractal refers to something like fractions, indicating that “a whole is an analogue of its part.” The opposite statement, “a part is an analogue of a whole” is also correct in the fractal theory.

(2) The adjective “stochastic,” is used to express blood concentrations of nutrient or antioxidant molecules (Table 1). The word stochastic means to be “deterministic” in Euclidean geometry, indicating the blood concentration can be predicted as an already known fact. However, in modern non-Euclidean geometry, stochastic means that prediction is impossible; however, if one looks at the whole, speculation is possible under a certain theory of probability.

Let’s now look at the above 2 main concepts: (1) the fractal theory, i.e. “a part is an analogue of a whole,” and (2) stochastic, i.e. “speculation is possible (to some degree) under a certain theory of probability.” We do it just like holding the 2 concepts against the sky and trying to see through.

Consequently, we will see a modern type of change over time in the blood concentrations of drugs, nutrients or antioxidants. It may be very stochastic, and 100% prediction may not be easy or possible. Although the liquid component of blood (plasma) accounts for only 1/12th (2.5 kg or 5% in a person of 50kg) of the entire volume of water in the body and 60% of the body weight (for example, 30kg in a person weighing 50k), it is a small window for us to have a full view of the person’s body. Therefore, the fractal theory, considering a part as an analogue of a whole, supports the validity of the speculation on the whole body through observations of the blood concentrations over time.

This fractal theory that assures the relationship between a part and a whole is a relational theory for space in non-Euclidean geometry, but space may be substituted by time.

If this substitution is possible, retrospective observation along the time axis would also be possible. We therefore analyzed the relationships between a huge amount of previously accumulated data and the recent data on blood/tissue concentrations of antioxidants and other substances (such as AHCC).

This means that it can be applied not only to spatial distribution, like that of the blood concentration of a substance, but also to time distribution.

In this way, we are able to predict the future beyond the two-dimensional horizontal axis from the blood concentration, based on the relationship appearing in front of us. It is very beneficial for a patient’s body because we can predict the future after 1, 3 or 6 months of administration of a specific amount of an antioxidant, and in addition, very useful information can be provided to patients with the same disease, people in certain areas or certain countries, and even the entire human population.

Note 2: The great philosopher and mathematician of ancient Greece, Euclid, was in Latin, was possibly called by this name among ancient Greek academics. However, the equivalent English name, Euclid, is also now well known. As he is considered to have lived during 365-275 BC of the ancient Greek era, he must have lived up to 90 years old. His life was 10% longer than the average life span of 82 years for modern Japanese men, so he must have been a man of great longevity in his time. Of course, this is only based on the assumption that the years of his birth and death are correct.

References


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<th>Table 1 Comparison of analytical methods in pharmacology</th>
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<td>Field</td>
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<tr>
<td>2次元空間 Geometry</td>
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<tr>
<td>3次元空間 Topology</td>
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<tr>
<td>抜散Diffusion</td>
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<td>血中濃度 Kinetics</td>
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<td>体内移行 Dynamics</td>
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The 17th International Symposium of AHCC Research Association

Date: July 25 (Sat.)–26 (Sun.), 2009
Venue: Hotel Royton Sapporo

Chairmen:
- Masuo Hosokawa (Prof. Emeritus, Hokkaido University)
- Masatoshi Yamazaki (Prof., Faculty of Pharmaceutical Sciences, Teikyo University)
- Yasuo Kamiyama (Prof. Emeritus, Kansai Medical University)
- Yutaka Mizushima (Vice President, Kyoai-kai Hospital)

Keynote lecture: Dr. Richard J. Andrassy
University of Texas Health Science Center

Sponsor: The AHCC Research Association
Support: Hokkaido Bureau of Economy, Trade and Industry
Amino Up Chemical, Co., Ltd.

The Latest Publications and Academic Presentations

*Presenting the titles of research that have appeared in international journals and academic conferences so far this year.

**Publications**

  "The Supplementation Therapy of Canine Dermatology in My Hospital"
  Manoru Onuma, Sadaharu Ono, et al.
  (Nihon University, Onuma Animal Hospital)

  "Inhibitory Effects of Oligonol on Phorbol Ester-Induced Tumor Promotion and COX-2 Expression in Mouse Skin : NF-κ B and C/EBP as Potential Targets"

- **The Journal of Nutrition Nutritional Immunology, 139: 598–602 (2009)**
  "Oral Administration of Active Hexose Correlated Compound Enhances Host Resistance to West Nile Encephalitis in Mice"
  Shuhui Wang, Tian Wang et al.
  (Colorado State University)

**Academic Presentations**

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The conference of the American Society for Parenteral and Enteral Nutrition (ASPEN) was held in New Orleans, U.S.A. for 4 days (February 1–4, 2009).

This year, Professor Anil D. Kulkarni, Department of Surgery, M.D. Anderson Cancer Center, The University of Texas, was the seminar moderator. The seminar was held on February 4 during Clinical Nutrition Week 2009, and there was a session on the theme “Dietary Substrates: Fruit and Plant” to introduce important supplements with scientific evidence for alimentary diseases and other dietary supplements.

In this session, Professor Toshinori Ito, Department of Complementary and Alternative Medicine, Osaka University Graduate School of Medicine, presented a wide range of basic and clinical data, including on AHCC and Oligonol, greatly attracting the attention of the audience. In addition, Professor Gil Hardy from New Zealand, and Professor Alejandro from Mexico talked about kiwi- and cocoa-related subjects, respectively.

Assistant Professor Hiroaki Yanagimoto, Department of Surgery, Kansai Medical University, held a poster presentation titled “Alleviating function of Active Hexose Correlated Compound (AHCC), a health food component, for side effect in chemotherapy patients” to indicate the effects of AHCC in mitigating the adverse effects of a chemotherapeutic agent, gemcitabine, in pancreaticobiliary cancer patients. In the study, the hemoglobin value after chemotherapy was significantly higher, the increase in serum c-reactive protein (CRP) in the blood was significantly smaller, and control of dysgeusia was significantly better in the AHCC treatment group.

At ASPEN, AHCC-related studies have been continuously presented by the University of Texas and Kansai Medical University over the last several years. In the field of clinical nutrition, proactive use of supplements is further expected and more study reports can be expected.

As it is not very cold this winter in Sapporo, we have less snowfall than average and feel physically relaxed, being free from the hard work of removing snow from the roads or our roofs. On the other hand, news reports of flight cancellations have increased greatly because of the snowfall at Chitose Airport, an entry point by airplane to Hokkaido. This is probably because the snow this year is well on account of the warmer temperature, in contrast to the powder snow that we usually have in Hokkaido, making it harder to remove the snow from airplane bodies and the runway. We always pay attention to return flight services for our business trips during this season, but this year’s situation is quite worrisome. In March, when we were busy editing our newsletter, we heard that spring had set in in Honshu (main island), making us feel that we may not, after all, have to worry about the snow any more. However, we also heard about the chances of heavy snowfalls in Hokkaido even in March: spring is still far away for us. The Secretariat has started preparations for the International Symposium of AHCC Research Association. We are looking forward to the summer when the symposium is held.

(Takehito Miura)