Intestinal Permeability and Its Role in Disease

By David Lescheid, PhD, ND

Maintaining integrity in the gastrointestinal (GI) tract is of paramount importance in our overall health. The commonly recognized functions of the GI tract (digestion, secretion, absorption, and motility) can occur effectively only if there are intact epithelial membranes. These functions must occur properly to provide us with the nutrients that we need to support our activities of daily living.

The mucous membranes of the GI tract also provide compartmentalization, protecting the relatively fragile, homeodynamic internal milieu from the relatively harsh environment of the intestinal lumen. Mucosal membranes include many different structures and cells with unique roles in maintaining the physical, chemical, and immunological barrier functions.[1]

Another major function of the GI tract is immunity. The epithelial cells of the GI tract provide the first line of defense, protecting us from the potentially dangerous or foreign substances brought into our body via our food and drink. Furthermore, most pathogenic microbes, including many medically important viruses,[2] must cross a mucosal barrier to cause disease. It is estimated that up to 80% of the immune system cells are initiated in the GI tract or spend a good portion of their life there. The gut-associated lymphatic system (GALT) is part of an interdependent mucosal immune system termed the mucosa-associated lymphatic system (MALT). Immunocompetent cells that develop in the GALT are transported via the lymphatic system to the circulatory system to be carried to other mucous membranes, such as the respiratory and urogenital tracts, to provide protection. This interdependence between all mucous membranes in the body is important because it means that by using bioregulatory medicines to restore integrity in the GI tract, we can influence the overall immune system and general health.

The immunological barrier function is a very dynamic and complex one, with roles not only in protection from substances that are foreign and/or potentially dangerous but also in tolerance to commensal microflora and the nutrients that are digested and absorbed to maintain normal body functions (Figure). In the healthy GI tract, with intact mucous membranes, tolerance is the predominant immunological function. Therefore, we do not react to the daily nutrients that we need to support our physiological functions. If the GI tract barrier is compromised, there is a breakdown in tolerance, leading to increased reactivity, chronic activation of immune system cells, and production of cytokines that can have localized and systemic effects.

Some of the more common diseases associated with a breakdown in the integrity of the GI tract include the inflammatory bowel diseases[3] and certain autoimmune diseases, such as ankylosing spondylitis, IgA nephropathy and multiple sclerosis,[4] type 1 diabetes mellitus,[5] and autism.[6] Other conditions associated with a hyperpermeable GI tract include congestive heart failure,[7] chronic venous insufficiency and the development of leg ulcers,[8] major depressive disorder,[9] chronic fatigue immune deficiency syndrome,[10] gallstones,[11] and progression of human immunodeficiency virus (HIV) infection.[12] The documented relationship between a "leaky gut" and so many important diseases, as described, speaks to the importance of medical interventions that can safely and effectively promote healing in a timely manner. This article will describe

the scientific support for the use of antihomotoxic medicines in treating a hyperpermeable GI tract and restoring optimal health.

Using homotoxicology to treat a hyperpermeable GI tract

One of the inherent strengths in homotoxicology is that it provides a very well thought out, logical approach to the progression of diseases and of disease regression. The Disease Evolution Table (DET) outlines a framework from which to position a disease in relation to its status of regulation and deregulation and to which germ layer of tissue has been affected. It also provides a relative guide as to the prognosis of the disease and the phases that might occur during healing. On the DET, a leaky gut is classified on the vertical axis in the section on endodermal tissue, just to the right of the regulation/compensation division in the impregnation phase. It means that it will take some time to restore gut integrity and that all 3 pillars of homotoxicology (i.e., organ regulation and cellular activation, immunomodulation, and detoxification) will have to be used to provide complete resolution.

In any disease, it is important to first examine the broader picture and ask what external influences might be contributing to the disease or acting as obstacles to cure the disease. For example, we know that many substances (e.g., gluten, certain food additives, heavy metals, and inhalants) affect the permeability of the GI tract. Microbial infections and aging also can increase permeability. Excessive, regular consumption of alcohol[13,14] and high fructose corn syrup[15] are also associated with the development of a leaky gut in susceptible people. It is important to discontinue this external supply of toxins as a first step towards resolution. Discontinuing these toxins supports the 4-S approach to detoxification: *Stop* (the external supply of toxins), *Support* (the organs of detoxification and drainage), *Stimulate* (elimination of toxins), and *Sensitize* (the patient for detoxification). Other toxins that affect the permeability of the GI tract include pharmaceutical drugs, such as proton pump inhibitors[16] and nonsteroidal anti-inflammatory drugs (e.g., cyclooxygenase [COX] 2 inhibitors).[17,18] Zeel has been shown to be as effective as COX-2 inhibitors in a clinical trial of patients with mild to moderate arthritis of the knee.[19] There are numerous clinical trials demonstrating that topical Traumeel effectively manages pain in many different musculoskeletal disorders, including acute symptomatic treatment of tendinopathy.[20] These studies suggest that antihomotoxic medicines can be used as anti-inflammatory agents that will not damage the GI tract.

The permeability of the GI tract is not only affected by physical toxins, but also by lifestyle events or stressors on mental or emotional levels.

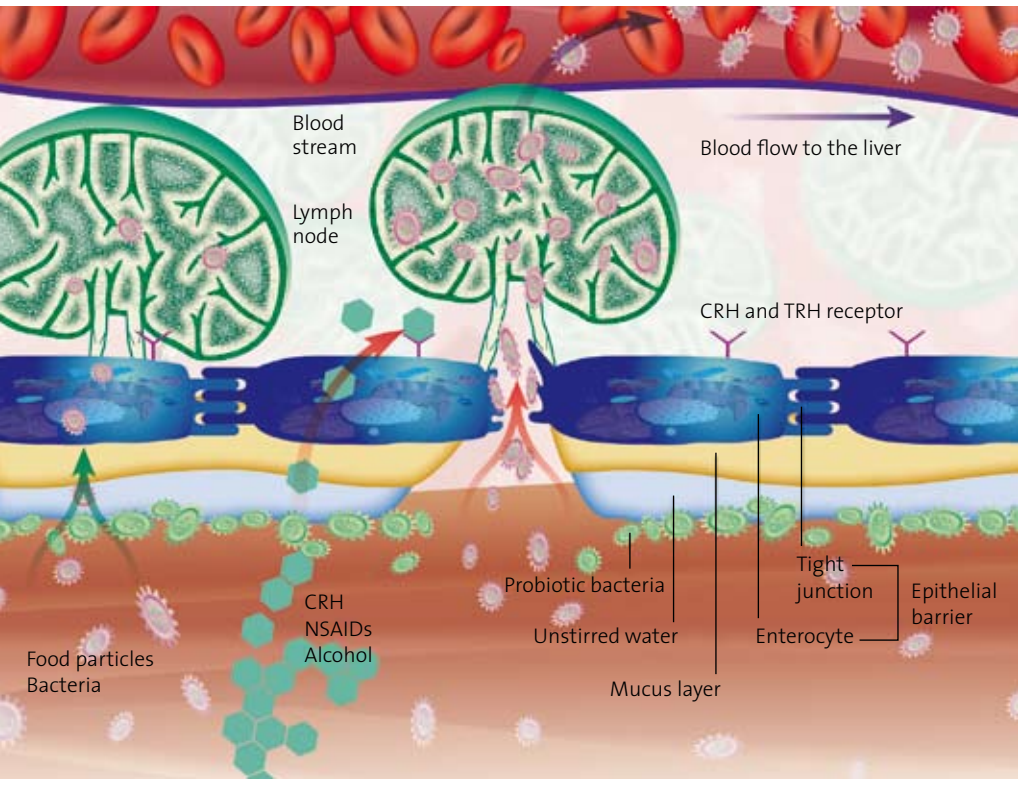


Figure. Intestinal mucosa. The mucosal barrier prevents harmful substances (e.g., toxins, pathogenic bacteria, and inflammatory mediators) from entering the body. At the same time, it serves as a highly selective filter, ensuring the absorption of useful substances (e.g., food particles) through tight junctions and epithelial cells.

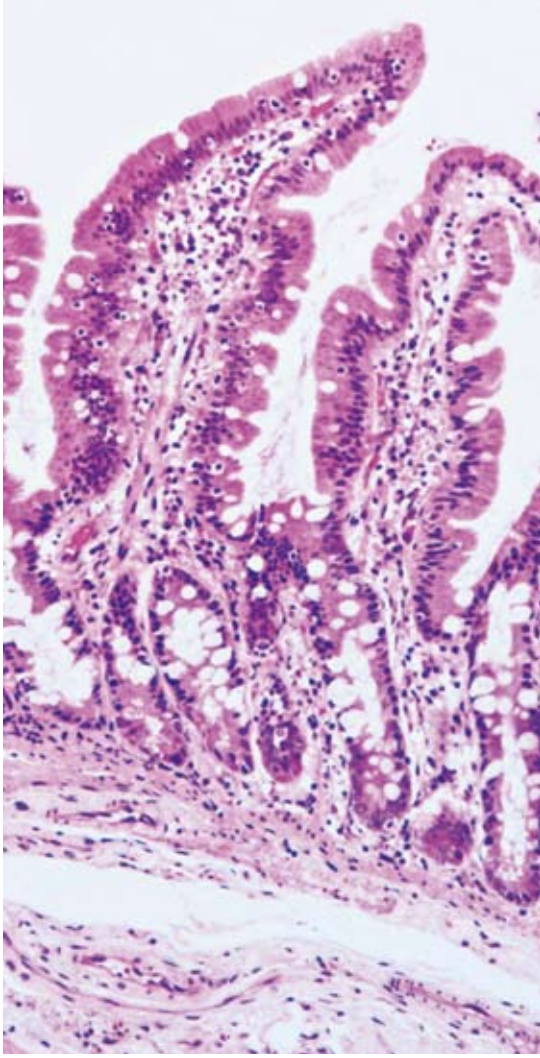
Abbreviations: CRH, corticotropin-releasing hormone; NSAID, nonsteroidal anti-inflammatory drug; TRH, thyrotropin-releasing hormone.

For example, it has been shown that even a short period of sleep deprivation in mice will cause a profound change in permeability of the GI tract and translocation of bacteria to normally sterile sites, such as the mesenteric lymph nodes, spleen, pancreas, and blood.[21] Chronic insomnia in humans is also associated with the production of proinflammatory cytokines and the reduction of antioxidant systems and hormones that can lead to hyperpermeability in the GI tract.[22] Neurexan is an antihomotoxic medicine that is useful in treating insomnia and helping to relax persons who are overstimulated by the stressors of daily living.[23] Modulating stressors, such as insomnia, can be an important part of treating a leaky gut because it has been shown in animal studies that chronic psychological stress will cause hyperpermeability in the GI tract and predispose the animals to hypersensitivity and illness.[24,25]

We have known for years that there is a connection between the nervous, endocrine, and immune systems via shared signaling molecules, receptors, and anatomical locations.[26,27] This field of psychoneuroimmunology has provided the scientific proof that there is a gut-brain connection and that physiological or pathological changes in one of these organs profoundly influence the function of the other organ. Recently, a parasympathetic anti-inflammatory pathway has been described; this pathway connects the cytokine signals in the GI tract with vagus nerve fibers, the brain, acetylcholine and its receptors on macrophages, and further changes in cytokine signals.[28,29] This pathway, termed the *cholinergic anti-inflammatory pathway*, provides the evidence needed to support the role that modulating parasympathetic nervous system output from the brain can play in healing the leaky gut. Several effective methods of modulating this pathway include acupuncture, biofeedback, mindfulness meditation, various forms of physical therapies, and chiropractic techniques.[28,29] Furthermore, there are a number of antihomotoxic medications that have been shown to be very effective in modulating the psychosomatic influences on disease states. These include Nervoheel, for anxiousness and irritability[23,30]; Neuro-Injeel/Neuro-Heel, for deeper pathologies, particularly for someone who has never been well since a specific life event; and Tonico-Injeel/Tonico-Heel, for physical and mental exhaustion from overwork.[23]

Correcting any dysregulation in the brain is an important component of healing a leaky gut. This healing can occur indirectly by modulating shared signaling molecules, such as cytokines, between the organs, as described previously. Alternately, this restoration can occur directly because there is recent evidence that physical structures previously thought to be found only in the central nervous system are also found in the GI tract.[31] This is the so-called brain-gut axis. It is suggested that "cellular interactions previously thought to be unique to the blood-brain barrier, also regulate gut epithelial permeability."[31] This evidence provides further support to the potential of using medicines commonly considered to be nervous system specific as adjuncts to healing the GI tract.

Once the external factors contributing to the development of a leaky gut, or interfering with self-regulation, have been identified and addressed, it is important to begin treatments using the 3 pillars of homotoxicology.



Cross section of gut mucosa

1. Organ regulation and cellular activation

There are a number of different antihomotoxic medicines that will support and regulate the organs of the GI tract. One of the key structures contributing to the physical barrier function of the GI tract is the tight junction between the epithelial cells. These tight junctions ensure that most of the substances that are absorbed follow the intracellular pathway rather than the paracellular pathway. By following the intracellular pathway, they are carefully processed by the intracellular enzymes and biochemical pathways of the epithelial cells before they enter the lymphatic or circulatory systems to be carried to the rest of the body. Two important processes in GI epithelial cells are the cytochrome P450 enzyme sys-

tems,[32,33] which are involved in the phase I and phase II detoxification of substances; and the p-glycoprotein and cation/anion transporter systems,[34,35] which act as phase III transporters regulating the influx and efflux of certain drugs, metals, and toxins. The function of both of these systems can be supported by Mucosa compositum. Furthermore, these intracellular processes are energy dependent and, therefore, the use of Coenzyme compositum is indicated to help support the Krebs/tricarboxylic acid cycle generation of adenosine triphosphate (ATP).

The tight junctions are also complex, dynamic structures that can be influenced by many different types of stimuli,[36] possibly including antihomotoxic medicines. A breakdown in the integrity of tight junctions has been associated with many different diseases.[37] The tight-junctional complex consists of a number of different proteins, including zonulins, occludins, and claudins; a number of different kinases; and a junctional adhesion protein, which is a member of the immunoglobulin superfamily.[38] The claudins and the occludins form extracellular loops that span the gap between the cells. The claudin proteins are water-filled pores that carefully select substances that enter the paracellular pathway based on charge and size. Zonulins act as tethering proteins linking the claudins to the intracellular matrix via their attachment to actin and myosin. This structural arrangement of the tight-junctional complex means that changes in the intracellular matrix, via actin-myosin interactions, can affect the opening and closing of the claudin pores and, therefore, the integrity of the epithelial barrier. The myosin heads have ATPase activity and, therefore, hydrolyze ATP to provide the energy to help them move along the actin strands.[39] This energy-dependent process can be supported by the use of Coenzyme compositum, an antihomotoxic medicine that is thought to generate ATP via its influence on the intracellular Krebs/tricarboxylic acid cycle.

2. Immunoregulation

If the tight-junctional complexes become permeable, macromolecules, including substances in food and drink that have not been thoroughly processed and microflora and their endotoxins, cross into the supporting aerolar connective tissue and interact with the immune system cells located there. These interactions result in the synthesis and secretion of inflammatory cytokines, such as interleukin (IL) 1β, tumor necrosis factor (TNF) α, and interferon γ. These cytokines also directly affect the tight-junctional architecture to further increase permeability.[38,40] A positive feedback loop is set up, with increased intestinal permeability up-regulating the synthesis and secretion of proinflammatory cytokines that increase permeability even further. Reversing a leaky gut requires repairing the physical tight-junctional structure, as described previously, in addition to modulating the inflammatory cytokines that are further impairing the healing process. According to a number of animal and human observational studies, it appears that the actual physical damage to the mucosal epithelial cell barrier occurs prior to the induction of excessive proinflammatory cytokines.[41] This further strengthens the importance of structural and functional organ support, as described previously, as an initial strategy to treating the leaky gut.

Once substances have crossed the mucosal epithelial cell barriers, antigen-presenting cells (e.g., dendritic cells) collect them, process them, and present them to naïve T cells. Depending on the nature of these substances, their dose, and the extent of interaction, different types of cytokines are synthesized and secreted. These cytokines influence the direction of T-cell development towards either T-helper cell type 1 (Th1)-dominant (cell-mediated) immunity or Th2-dominant (humoral) immunity. Other T cells, termed Th3 and/or Treg cells, play a role in ensuring that the immune system shift in either direction is moderated and not too vigorous or persistent. A detailed description of Th1/Th2/Th3/Treg immunity is beyond the scope of this article and is reviewed in detail elsewhere.[42-45]

An enhanced understanding of the cytokines involved in the pathogenesis of various diseases will assist in the development and use of safe, effective methods of modulating these cytokines and recreating balance in the immune system to promote healing. Immunomodulation is an important step in the healing of the leaky gut.

Two of the most important cytokines directly contributing to increased permeability in the GI tract are IL-1β[46] and TNF-α.[38] There are a number of specific targets for these cytokines in mainstream medicine, including the monoclonal antibodies to TNF-α, infliximab and adalimumab; however, both of these medicines have a substantial number of potentially severe adverse effects.[47] A safer, effective way to modulate these cytokines is by using the antihomotoxic medicine Traumeel. Using in vitro studies, the extent of modulation of TNF-α and IL-1β by Traumeel is significant, ranging from 54% to 70%, respectively.[48]

Echinacea compositum is an antihomotoxic medicine that has been shown to effectively prevent postoperative infections.[49] There is re-

cent evidence that the alkylamides from extracts of the root of *Echinacea* species modulate TNF-α, via the endogenous cannabinoid receptors.[50,51] The *N*-alkylamides of *Echinacea purpurea* work synergistically to not only decrease the expression of TNF-α but also to increase the expression of IL-10,[52] a cytokine known for its immunosuppressive effects on Th1-dominant diseases such as Crohn's disease.

Because of the ability of *Echinacea* extracts to shift the immune system towards Th2-dominant immunity, it is important to use them with caution and only in conditions in which they are unlikely to aggravate signs and symptoms. For example, ulcerative colitis is considered a Th2-dominant disease[53] and, therefore, any medical intervention (e.g., with *Echinacea* extracts) that promotes further development of Th2 cells might cause an aggravation of symptoms. Furthermore, persons who are sensitive to plants in the Asteraceae family also might be sensitive to *Echinacea* extracts. Finally, because *Echinacea* species extracts, in particular the aerial parts, have immunostimulatory activity, it is suggested that they are not administered in full concentrations to persons with autoimmune conditions. A homeopathic concentration of D4 (1:10,000) is considered safe for oral use and, therefore, the use of Echinacea compositum drinking ampoules is safe in autoimmune and proliferative conditions.

Even before substances in the GI tract lumen reach the epithelial cells or tight-junctional complexes, they must diffuse through a mucous layer. The mucous layer is not simply a static physical structure. It is highly dynamic, with a meshwork of many different interdependent proteins and carbohydrates. Two of the best-characterized components of the mucous layer are trefoil factor peptides (TFFs) and mucin.[54] Both of these components are synthesized and secreted by the goblet cells interspersed throughout the mucous membrane. They migrate onto the luminal side of the epithelial cells to provide an extra viscous layer of protection and selective filtration.[55,56] The synthesis and release of TFFs is diurnal, with a peak time during the nocturnal hours. This protective rhythm is disrupted by aging, a *Helicobacter pylori* infection, sleep deprivation,[57] and celiac disease.[58] Furthermore, there is evidence that modulating proinflammatory cytokines, such as TNF-α, also helps maintain optimal levels of TFFs,[59] suggesting that this might be another mechanism by which Traumeel can act to help in the restoration of gut integrity.

3. Detoxification

Once the organs of the GI tract have been supported and the proinflammatory cytokines have been modulated to the point at which they can self-regulate, it is important to ensure that all remaining endotoxins and exotoxins are detoxified and drained. Clearing toxins also helps to activate physiological systems that protect the GI tract from further damage. In addition to the TFFs, another important component of the mucous layer is mucin. Mucins are large extracellular proteins that are heavily glycosylated with a bottle brush-like structure. The mucins play a number of roles, including control of cell growth, signal transduction from the lumen to the intracellular structures, adhesion of commensal and potentially pathogenic microbes, and protection.[60] Their protective function is due in part to the ability of the glycoproteins to act as a molecular sieve, carefully regulating diffusion of substances based on their charge and size. For this careful, selective process to occur optimally, the mucins need to be relatively free of toxins. Furthermore, regulating proinflammatory cytokines also helps mucins to assemble and function appropriately.[61] It can be postulated that using Lymphomyosot and Traumeel might help to keep the mucin structures clear and able to perform their functions optimally; this is an important contributing factor to healing a hyperpermeable GI tract.

Many of the immune system cells of the GALT are present in the loose areolar connective tissue just below the epithelial cells.[1] For these immune cells to work optimally, there must be a relatively clear pathway for antigens to be able to be received by them. Furthermore, these immune system cells must have a relatively high degree of mobility to move to where they are needed to mount an appropriate immune response. In my opinion, using drainage preparations, such as Lymphomyosot, may help keep this loose areolar connective tissue relatively free of exotoxins and endotoxins; this is an important part of ensuring that an appropriate immune response occurs.

It is important to recognize that there is a closely regulated, interdependent relationship between the GI tract and the liver. The stomach, intestine, spleen, and pancreas drain to the liver via the hepatic portal system. Therefore, many of the toxins from a leaky gut will end up in the liver, where they need to be processed. Furthermore, if the detoxification mechanisms in the liver are not functioning adequately, excess or insufficiently processed toxins are recycled back into the duodenum of the GI tract via the bile duct. Using Nux vomica-Homaccord or Hepar compositum to support liver detoxification systems and Coenzyme

compositum to support the energy demands of these systems is thus important. The addition of Berberis-Homaccord reduces the toxin burden even further by supporting the detoxification and drainage functions of the kidneys and liver. Animal studies[14,62] have shown that excess alcohol consumption causes direct damage to hepatocytes and leads to the development of a leaky gut. The increased toxin load, subsequent to this increased GI tract permeability, further contributes to liver damage, stressing the importance of addressing the health of the liver and GI tract simultaneously.

Conclusions

Because of the paramount importance of the mucosa in systemic immune responses and the connectivity between all of the mucosal barriers in the body, repairing a leaky gut can be an important access point in the management of many diseases. Management begins by discontinuing the intake of potentially damaging toxins or lifestyle choices and replacing or repairing them with antihomotoxic medicines that will not cause any further damage. It is important to support the ability of the various organs to perform their physiological functions (using Mucosa compositum, Nux vomica-Homaccord, and Coenzyme compositum) and to immunomodulate cytokines, such as IL-1β and TNF-α (using Traumeel and Echinacea compositum). This will halt the positive feedback loop of increased permeability, production of excess proinflammatory cytokines, and further permeability. It is also important to recognize that there is a definitive gut-brain connection and, therefore, it is essential to address any mental and/or emotional disturbances (using Neurexan, Neuro-Heel/Neuro-Injeel, Nervoheel, or Tonico-Heel/Tonico-Injeel) that could be interfering with restoration of mucosal integrity. Finally, it is important to remove toxins and to activate the organs, so that they maintain optimal detoxification pathways even after therapy has been discontinued.

The science and art of homotoxicology provides us with a scientifically supported, logical framework to heal a hyperpermeable GI tract and, therefore, support maximal health in our patients. One of the additional strengths of antihomotoxic medicine is that the medications can be used synergistically with other natural health products to support timely and effective healing. Other natural health products shown to be useful in healing the leaky gut include probiotics,[62-64] quercetin,[65-68] L-glutamine,[69-71] zinc,[72-74] zinc carnosine,[75] vitamin A,[76] vitamin D,[77,78] melatonin,[79] curcumin,[80-83] and licorice extracts.[84]

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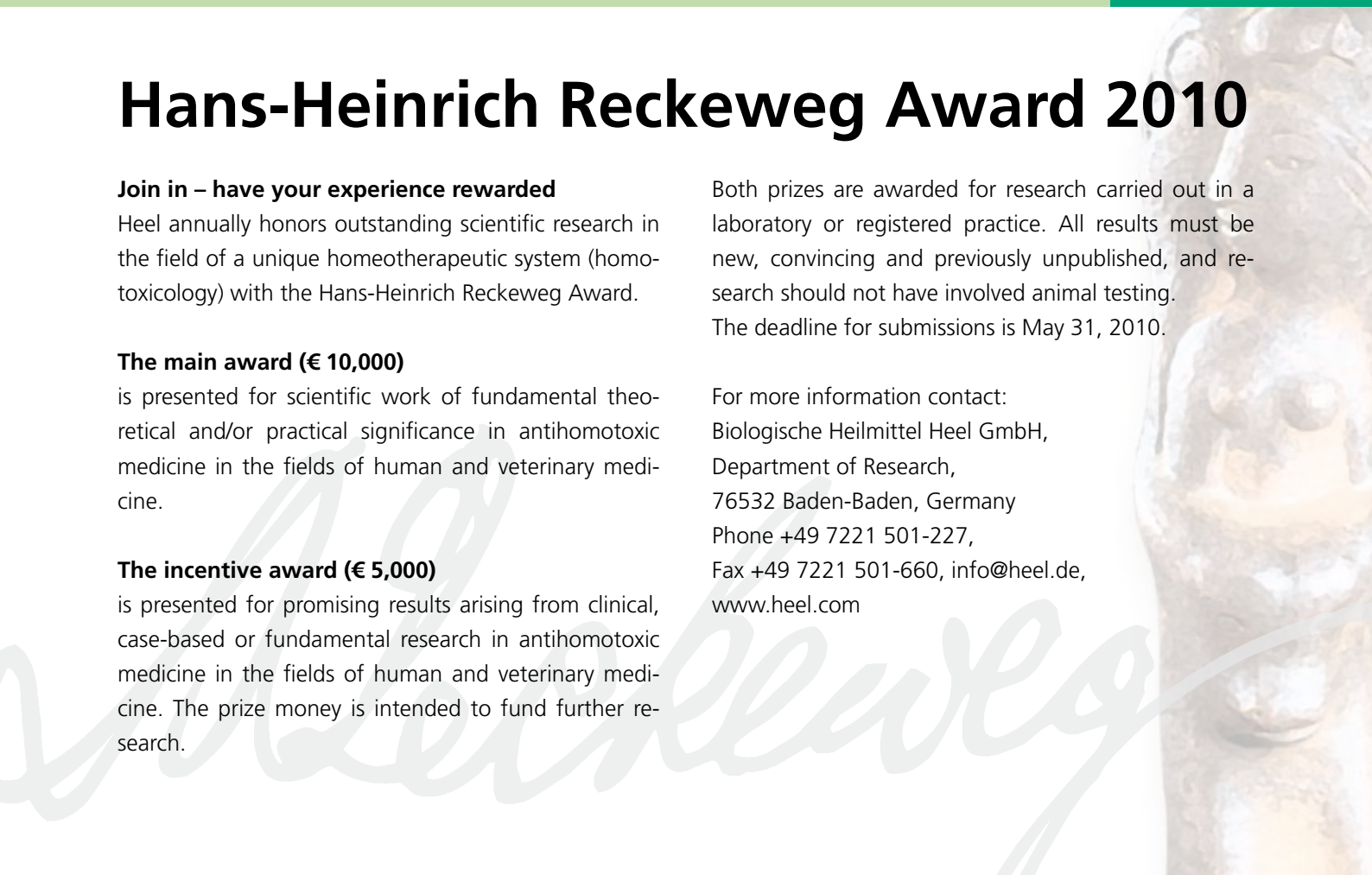

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