The Mode of Action of Bacterial Remedies

A new concept of Bacterial Medications made from Metabolic Products offers practitioners a smart and safe way to modulate immune function

By Ronald Ullmann, biochemist
Syntrion GmbH, Calw, Germany

For many years, immune modulation therapy has been used to help patients fight acute and chronic conditions. Major goals of this therapy are to 1) enhance overall immunological reactivity in case of suppression and 2) balance an overactive, excessive immune response to restore healthy, normal function. Immune modulation treatment also increases the readiness and capabilities of the immune system in cases of chronic infection, and provides greater protection against infections during cold season, such as by taking Echinacea.

In some cases, the objective is to increase response, while in other patients the therapy must reduce activity to a less reactive level. As a rule, health care practitioners always wish to influence their patients' immune function positively without inducing an inflammatory or provoking immune reaction. Here it is important to point out that giving the patient a harsh microbiological therapy will induce a strong reaction. Yet proper immune activity requires a balanced response. As a result, one counter-indication would be use of whole cell or cell wall preparations as a general therapeutic tool in suppressing an overreactive immune response.

HOW THE IMMUNE SYSTEM WORKS

To function properly, the immune system must 1) recognize a microorganism or toxin that could have a negative impact on the human body; 2) have the capability to discriminate between self and non-self; and 3) create an adequate response that is neither an underreaction nor an overreaction. If the immune system reacts too strongly, it can lead to a much more harmful effect on the body than that caused by the microbe or toxin itself.

The white blood cells (WBCs) originate from stem cells in the bone marrow. WBCs cells are divided into two types depending on the number of cell nuclei: mononuclear (one nucleus) and polymorphonuclear (more than one nucleus).

Mononuclear WBCs consist of macrophages and lymphocytes. Macrophages that reside in the tissues are called histiocytes. Moreover, lymphocytes are separated into two populations, the B cells and T cells, which also subdivide into additional categories.

Polymorphonuclear cells include eosinophils, neutrophils and basophils, which can only be distinguished from one another

Cells Of The Immune System And Their Specialized Functions

Lymphocytes
B-cells:
production of antibodies

Tc (cytotoxic) cells
elimination/inactivation of infected cells

Th (helper) cells
coordinate the immune response by direct cell-to-cell interactions and release of cytokines

Phagocytes
inactivate infectious agents or foreign pathogens by internalization

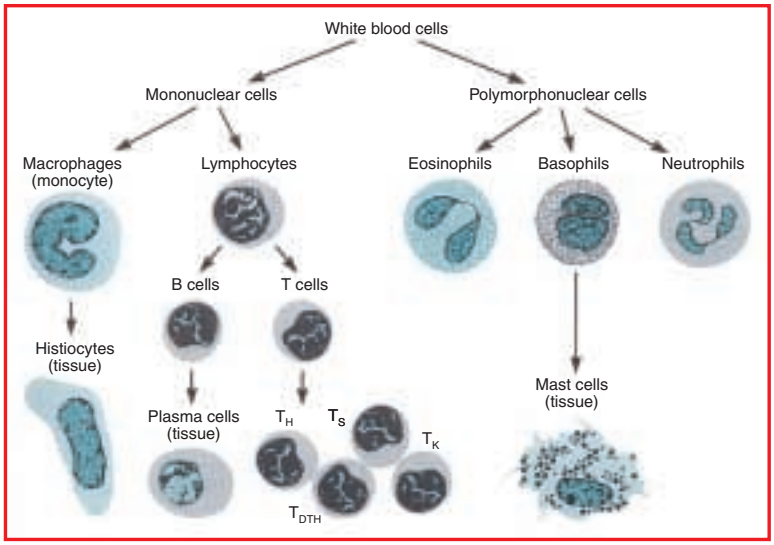


Image from Immunology, Immunopathology and Immunity, Stewart Sell, ASM Press, 2001

by staining techniques. Each of the cells has different functions in the immune system, but share the job of eliminating foreign invaders.

When a pathogen enters the body, the immune cells must recognize and act against it in a regulated manner to eliminate the invader without harming the host. This complex reaction occurs in two ways. The first is the **NON-ADAPTIVE IMMUNE RESPONSE (Nonspecific)** which has no specificity to eliminate microbes. Macrophage activity offers a prime example of Nonspecific immune function. The macrophage recognizes a bacterium, attaches to and wraps a piece of membrane around it, internalizes the germ and secretes molecules into the compartment that destroys the bacterium. This process is called phagocytosis, and a compartment is required because the secreted molecules are toxic to the macrophage itself.

If a macrophage is capable of destroying a bacterium on its own, it communicates with other immune cells to let them know it does not need help. The macrophage always reacts in the same manner each time it encounters a bacterium, irregardless of whether it has been exposed to the germ previously.

If the Nonspecific function responds efficiently to a microbe, the body does not require the **ADAPTIVE (Specific) IMMUNE RESPONSE** (or perhaps only a small reaction). However, if the first line of protection against a toxin or microbe is not sufficient enough, then the second, Specific line becomes activated. This cell-mediated response occurs when a B cell or T cell reacts to a certain epitope, or surface structure, on a microbe that the body wants to eradicate. One example of a Specific response is when a B cell produces antibodies that tightly bind to the epitope and eliminate the invading microorganism. The antibodies also act as a marker for all the cells that internalize the bacteria and inactivate them. A second example of a Specific immune reaction would be when a T cell binds to a human cell that has been infected by a virus (or is no longer regulated by neighboring cells), injects toxic molecules and destroys it.

A Specific immune response also creates cell memory, meaning that immune cells present in the body already know how to handle a microbe based on prior contact. If a particular bug invades the body once again, the immune cells that encounter the microbial antigen recognize it and respond rapidly by producing antibodies to meet the threat.

Immune Response

First	**- recognition of the pathogen or foreign material, and**
Second	**- a reaction to eliminate it**

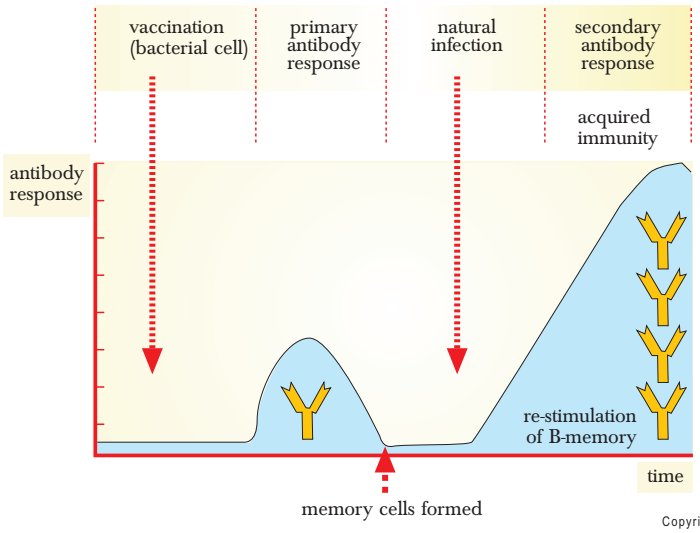
Innate immune response (Non-adaptive)

- not specific for a particular antigen
- does not change through repeated exposure to a given infectious agent

Adaptive immune response

- highly specific for a particular pathogen (specificity)
- improves with each successive encounter with the same pathogen

Vaccination



Principle of vaccination is based on two key elements of adaptive immunity

- specificity
- memory

Aim in the vaccine development: to alter pathogens or their toxins in such a way that they become innocuous without losing antigenicity

Re-stimulation of B-memory cells, which produce a faster and more intense secondary antibody response, thereby neutralizing the toxin

TWO TYPES OF COMMUNICATION

For Nonspecific and Specific immunity to work well and achieve a balanced response, the immune cells must communicate either via signalling molecules or direct cell-to-cell contact. In the first strategy, the macrophages internalize bacteria and release molecules called cytokines to let other cells know that they are eliminating the invaders. If the problem is too large, however, the macrophages send precise information about the microbe to the B cells and request antibody production, which bind to the invaders and inactivate them.

Specialized Functions Of Immune Cells

B – cells

- Lymphocytes
  production of antibodies
- Macrophages
  inactivation of antigens (e.g. infectious microbe) by phagocytosis

T – cells

- Tc cytotoxicity cells
  inactivation of infected cells (viral)
- Th helper cells
  coordinate the immune response by direct cell-to-cell interactions release cytokines (signalling molecules) that help B-cells to produce antibodies

The second mechanism involves direct cell-to-cell contact. Each cell has surface receptors that enable it to exchange information with other cells. For example, T cells communicate with B lymphocytes to allow the immune system to adjust its overall reaction against a toxin or foreign molecule. In addition, TH1 and TH2 helper cells coordinate the immune response, directing specific cells to kill foreign microbes and helping decide what represents an adequate response so as to prevent an overreaction.

The objective in both strategies is for an immune cell to let other cells know whether it can handle a pathogen located in the lymph, bloodstream and body fluids by itself, or if it needs help. Moreover, if an invader such as a virus incorporates into the genetic material of host cells, the body cannot recognize it because the cell's surface is the body's own material. To alert the immune system, the infected host cell protrudes receptors to its surface that provide information to the T cells, which then inactivate the host cell by injecting toxic molecules into it. If the mechanism does not work, a cancer process can take place. This difference in response to intracellular and extracellular pathogens is the reason why the immune system requires different mechanisms to deal with the various challenges it faces on a daily basis.

The most efficient defense is a highly effective Nonspecific response that readily handles a microbial invader or toxin because the infected person will not develop illness symptoms, such as the flu. If direct cell-to-cell contact takes place, it always results in Specific immunity sub-divided into a B cell and T cell response against the invader.

IMMUNE SYSTEM IMPAIRMENT

The consequences of an impaired immune system are seen everyday in medical practices. They include auto-immunity, immuno-deficiency and hypersensitivity of the immune system.

Autoimmunity occurs when a tiny protein part located on a germ's surface exactly resembles a structure on normal body cells. As a result, Specific immunity is developed against this tiny part, and B cells produce antibodies that recognize this protein piece on the surface. Unfortunately, the antibody will also attach to normal body cells carrying the same protein piece and destroy them.

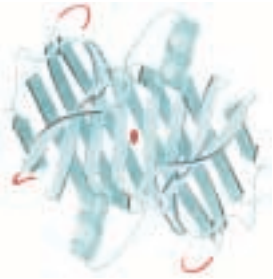
One example is **Candida albicans**, which has tiny protein pieces that closely resemble those on human cells. Scientific research conducted by ImmunoSciences Lab, Inc. in Southern California has shown that Candida albicans causes an Adaptive immune response with antibodies that

What Is Recognized By The Immune System

B-cells, T-cells and antibodies recognize parts of antigens (the epitopes) and not entire organisms or toxins

Molecules that are recognized:

- carbohydrates (structures on the surface of infectious microorganisms, e.g. parasites)
- proteins (structural parts of infectious microorganisms, e.g. anthrax, salmonella, viruses)
- toxins (toxic metabolic products from infectious microorganisms, e.g. cholera toxin)



are also directed against the ovaries, liver and other tissues. Although the immune system mounts a response to the Candida albicans, autoimmunity may result if cytotoxic T cells attack organ cells because they cannot distinguish between the microbe and the body's own cells.

This process is referred to as ***molecular mimicry***. It has also been reported for certain mycobacteria, which may work in the same way to cause arthritis and immune system dysregulation. It seems likely that molecular mimicry may result as a severe consequence if a preparation is used to initiate a Specific response when a Nonspecific modulation would be preferred.

...immune preparations that represented an appropriate choice 50 years ago are often too strong today due to lifestyle effects that have led to an overall more sensitive immune system.

Immune deficiency takes place when the overall reaction level is reduced, which prevents development of a proper response against an invading microorganism or toxin to rid it from the body. It can have an extreme effect on the body, such as the cholera toxin that causes severe diarrhea and can lead to death from dehydration if not treated properly.

Finally, **hypersensitivity** occurs when a microbe or toxin invades the body or comes in contract with the mucosa (nose or mouth), and the immune system mounts a huge reaction that causes more harm to the tissues than the pathogen.

The goal of any therapy, therefore, is to create a balanced immune response that eliminates the invading microbes or substances without harming the body tissues. In this sense, a Nonspecific or Specific response cannot be called good or bad, but instead must address the patient's particular situation so as to provide a proper response. On the other hand, if the immune system overreacts to an invading microbe, using an immune modulator as part of the patient's therapy must avoid further stimulation of a harsh immune response.

THE DIFFERENT TYPES OF IMMUNE MODULATION PREPARATIONS

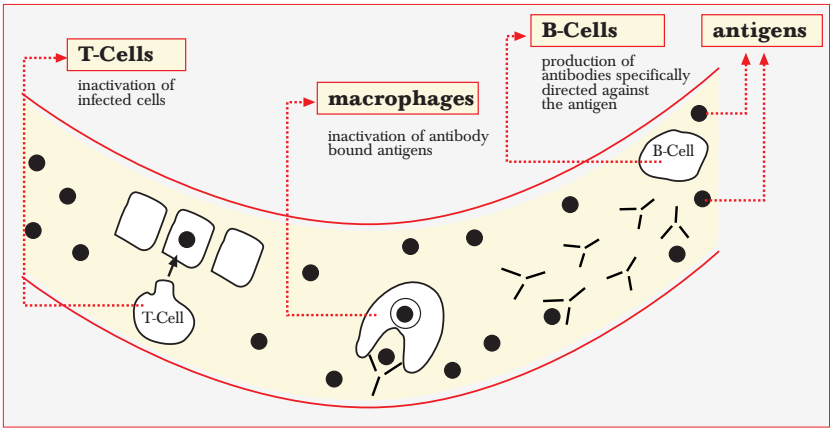
Medicine today uses different strategies to modulate immune function that evoke weak, intermediate or strong reactions. These include:

1) **Herbal medicines** such as Echinacea and Ginseng that trigger Nonspecific immune effects;
2) **Prescription drugs** designed to provoke Nonspecific and Specific (cell-mediated) effects, where B cell and T cell response comes directly into play;
3) **Whole cell or cell wall bacterial preparations** made from inactivated or killed microorganisms that mainly work on the Specific (cell-mediated) level. Because they contain antigens and can be strongly immunogenic, whole cell remedies often provoke harsh reactions;
4) **Metabolic Products from bacteria** that primarily trigger a Nonspecific immune response, but also secondarily create Specific and Anabolic effects, including mood enhancement. **A new type of therapy based on modern immunology, metabolic products consist of small molecules excreted by the bacterial cells that provide gentle immune modulation.** In addition, metabolic products are very different from the whole cell or cell wall preparation category first developed in the 19th century.
5) **Oral probiotics** that cause weak Specific, Nonspecific and intestinal microflora regulating effects. Probiotics normally have a smooth effect because it would not make sense for the body to react strongly against what it needs for health, such as the physiological microflora located in the digestive tract (e.g. Lactobacillus or Enterococcos).

It is essential to emphasize that **immune modulating therapy is indicated only in the case of an illness caused by the immune system**. The question must be asked: what is the reason for the immune suppression? For example, if a patient suffers from a secondary pancreas insufficiency known to depress immune function, it would not benefit the patient to stimulate an immune reaction because the immune system impairment is, in this case, a secondary effect, not primary.

Therefore, a successful therapy would focus on eliminating conditions that led to the secondary pancreas insufficiency. Other factors that include job and family stress, exposure to toxic molecules, free radical stress, lack of exercise and infections such as Candida in the intestines also can lead to significantly depressed immune function.

Specific Immune Response



Importantly, an appropriate diagnosis before and during treatment is absolutely required. Analysis of immune parameters – for example, in the blood – with clinically recognized methods performed by licensed labs often help determine the proper therapy. One example is the determination of secretory Immunoglobulin A (IgA) in the stool, which provides information about the health or reactivity of the gut-associated lymphoid tissue (GALT). Reduced values in the stool would indicate the need for microbiological therapy. In addition, levels of other molecules can be measured to determine whether the therapy would be more suitable to work on a cellular or non-cellular level.

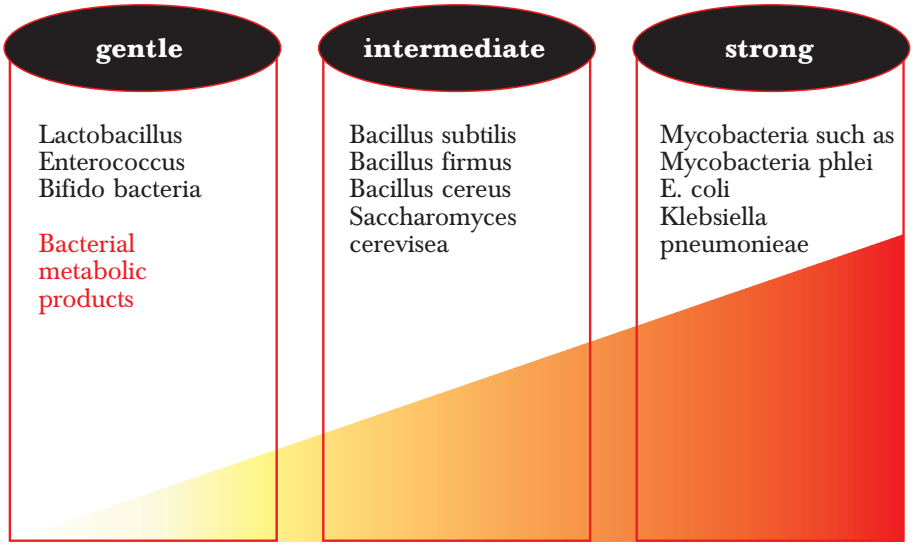
With immune modulation therapy, a general activation is less important than balance. An increase in T cell or B cell activity does not tell the practitioner much about whether a microbiological therapy is good or bad in terms of changing an overreactive immune system or enhancing a depressed one. For example, a severe TH1 to TH2 cell imbalance would not be eliminated through the IV injection of a whole cell or cell wall preparation, which exacerbates the problem. Instead, a preferred strategy based on modern immunological thinking is to gently support the immune system to eliminate stressors. Moreover, individual use of preparations depends on the patient's reaction condition. The more severely a patient reacts, the weaker the preparation that should be chosen. And as many practitioners know, some patients can be deficient and hyperreactive at the same time, reflecting the health status of the immune system's different parts.

IMPORTANT DISTINCTIONS BETWEEN REMEDIES MADE FROM WHOLE CELL (CELL WALL) AND METABOLIC PRODUCTS

Microbial therapy is based upon two concepts due to the nature of the microorganisms used. Historically, the development started with the introduction of whole cell and cell wall fragment-containing preparations. Recently, changing lifestyle conditions – notably poor nutrition, increased psychological stress, lack of exercise and

Immunogenicity Of Microbial Immunmodulators

Various antigens are also different immunogens, which means that they influence the immune system in a **strong, intermediate, or gentle manner.**



greater exposure to toxic substances – have led to generally weaker immune systems among the human population. As a result, a new approach in treating immune system disorders has become increasingly popular: use of bacterial therapy derived from metabolic products.

In general, attempting to weigh the value of a whole cell or cell wall fragment remedy against one made from metabolic products is much like comparing apples to oranges because the general mode of action is completely different. In terms of how it works, a whole cell or cell wall remedy – which can be considered a vaccine – significantly addresses the Specific, cell–mediated reaction as its primary immune effect, while a bacterial medication made from metabolic products mainly triggers the Nonspecific immune response. Both strategies have benefits and problems, and their application must depend on the patient's diagnosis and immunological situation.

Nonetheless, certain key distinctions can be made between the two possibilities or strategies used today to produce medications from bacteria.

Whole cell or cell wall bacterial preparations are derived from microorganisms either capable of or no longer capable of multiplying. Using inactivated microbes eliminates the risk of actually causing a disease in the patient, especially if a remedy is injected. Despite this cautionary step, some mycobacteria whole cell or cell wall preparations express immunogenic epitopes (proteins) on their surface that can cause the immune system to react very strongly. In fact, Mycobacteria whole cell or cell wall preparations have been reported to be very strong, immune system-provoking bacteria in contrast to, for example, bacteria of the physiologic microflora that provide gentle, beneficial immune modulation.

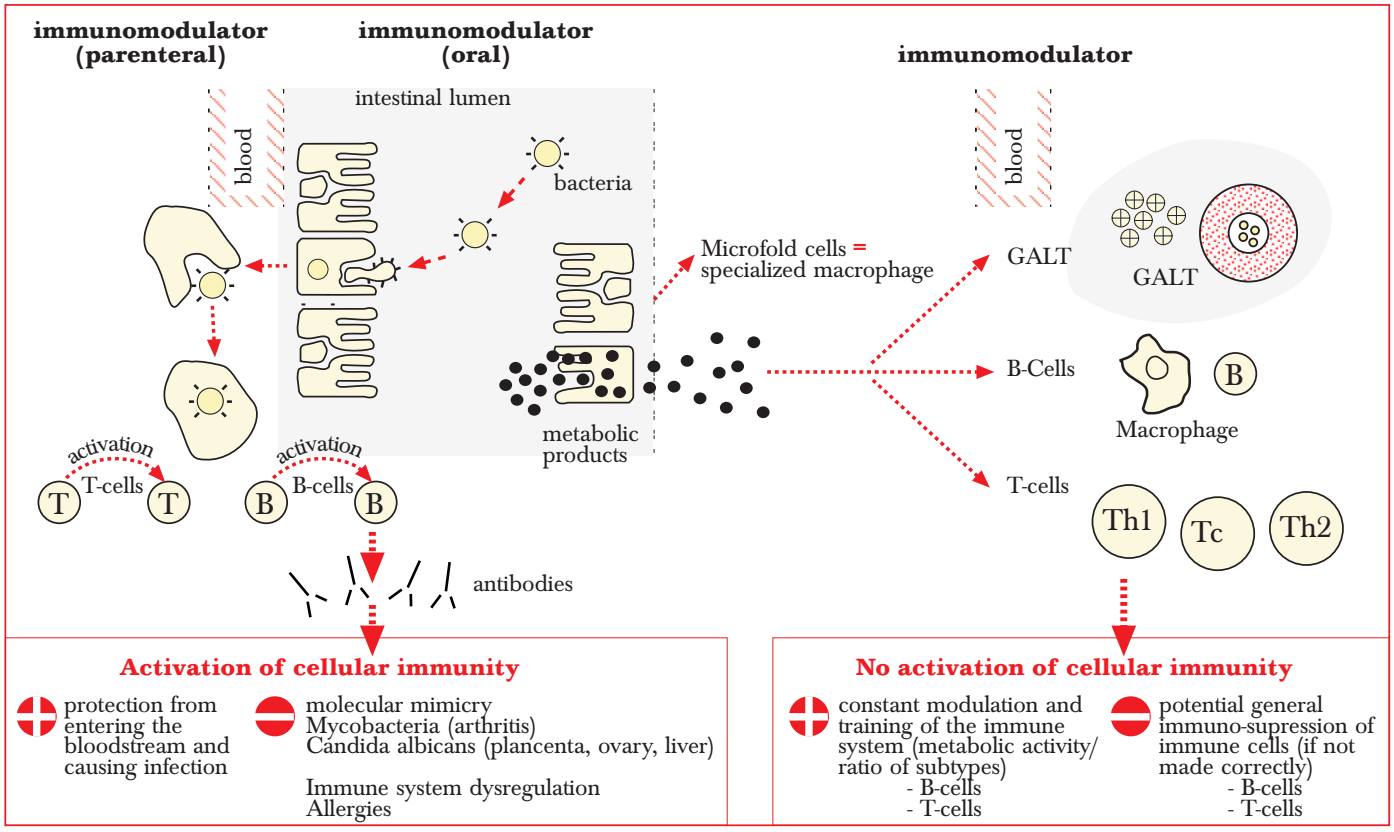
When a patient is administered a whole cell microbiological remedy, macrophages internalize the bacteria and present information on their surfaces. Using receptors, B cells and T cells recognize the information, resulting in the production of antibodies that vaccinate the patient against the specific germ being applied. In this respect, whole cell or cell wall preparations are vaccines.

When taken orally, the whole cell or cell wall preparation contacts the immune system in the intestine. Macrophages in the mucosal layer called M cells (M: microfold) take up the bug and pres-

Mode Of Action Of Microbial Therapy

Whole Cell Preparations

Metabolic Products



ent a tiny amount of the invader's cell surface information on their own surfaces to help the immune system identify it. T cells and B cells are activated and the immune response starts with production of antibodies against the presented information. A positive effect is that this process protects the body from the microorganism because the IgA defense mechanism resides in the intestinal mucosal layer. Before the microbe can enter the body, therefore, an antibody binds to and eliminates it. An example of this highly beneficial strategy would be protection provided against harmful microbes ingested with food while travelling to foreign countries.

On the other hand, whole cell bacterial remedies made from microorganisms that influence the immune system in a strong and intermediate manner – including Mycobacteria, Klebsiella, E.coli, various types of Bacillus and others – can mediate a very harsh and provoking reaction that does not represent the needs of the patient's immune system. Recent peer-reviewed publications have demonstrated that the effects of a "modern" lifestyle have significantly impacted the human immune system. **As a result, immune preparations that represented an appropriate choice 50 years ago are often too strong today due to lifestyle effects that have led to an overall more sensitive immune system.**

Administering certain types of whole cell or cell wall preparations even orally may carry considerable risks if not used properly. One negative effect is their potential to create molecular mimicry or anergy (unresponsiveness) under certain conditions of the immune system. In addition, their antigens also may cause severe inflammatory reactions by potentially contributing to an imbalance of the TH1 to TH2 cell ratio.

In contrast, properly made **bacterial remedies derived from metabolic products** in most cases contain no antigens and therefore eliminate the potential risks – dependent on the condition of the patient's immune system and the specific illness suffered – that may be caused by whole cell preparations' influence on the Specific immune response. Mycobacteria represent one example of the profound differences. Whole cell or cell wall forms of this type of bacteria always induce a strong Specific, cell-mediated reaction due to molecules expressed on the bacteria's surface. A Mycobacteria remedy made from tiny metabolic products eliminates this harsh reaction because it does not contain antigens

Metabolic products are low molecular-weight substances that mainly trigger a Nonspecific immune effect, but, in most cases, do not lead to a Specific or cell-mediated immune response initially. B cells and T cells may be activated or modulated to make them capable of eliminating an invading microorganism, but this is a secondary, not a primary, effect.

When taken orally, metabolic products of low molecular weight are <u>not</u> presented by macrophages to the B cells and T cells because they are too small (specific recognition of a molecule is also size dependent). Bacterial remedies made from metabolic products work on the GALT. Therefore, determining IgA levels before and following therapy can measure the effect. These preparations serve to activate macrophages and natural killer cells that internalize toxins, but at times may also mediate a T cell or B cell response. In most cases, metabolites work on the different sub-types of immune system cells without inducing Specific immunity initially, and may act in a stimulating, enhancing or suppressing mode.

Another important advantage of remedies derived from metabolic products is the constant training and modulation of the immune system, including the metabolic activity of the cells or the ratio of sub-types, such as B cells and T cells. On the other hand, if not correctly tested during remedy development, a negative effect can be that metabolites may cause a general immunosuppression when applied improperly. Accordingly, the safety and efficacy of all types of bacterial immune modulators can and should be demonstrated with toxicological and clinical studies.

...bacterial remedies derived from metabolic products in most cases contain no antigens and therefore eliminate the potential risks that may be caused by whole cell preparations...

To ensure this data is made available, European Regulatory agencies recently requested safety and efficacy testing for whole cell and cell wall preparations made from Mycobacteria, E. coli and other

types of bacteria. Companies unable to produce the required scientific data to support the claimed positive effect of oral and injectable bacterial remedies on the immune system may face elimination of their products from the European market.

METABOLIC PRODUCTS: A SMART AND SAFE CHOICE

In summary, the question is not which type or concept of preparation is "better." Instead, the success of immune modulation therapy is dependent on a precise diagnosis and analysis of a patient's indications. Nonetheless, it is vital to understand that in most cases a depressed immune system may NOT return to normal function by inducing a harsh inflammatory reaction. Such a reaction can occur with whole cell or cell wall preparations that possess strong or intermediate immunogenic potential due to the antigens located on the cell surface of the different bacteria. In terms of modern immunology, this is no proof of efficacy. For example, although they cause an immune response, certain infections cannot be considered beneficial for patients' health due to recently explored pathogenic mechanisms that include autoimmune disorders and molecular anergy.

It is also important to understand that whole cell or cell wall remedies and metabolic products produce different immune responses. Whole cell remedies primarily cause a Specific immune response, while metabolic products mainly mediate Nonspecific activity, enabling patients to boost their general level of immune activity when practitioners consider it desirable.

Editor's Note: SanPharma bacterial remedies – Cereus, Firmus, Mycobactin S and Subtilis – distributed by BioResource in North America are made from metabolic products. These medications represent the latest in modern immunological thinking and provide gentle immune modulation. SanPharma bacterial remedies do not contain whole cell or cell wall fragments.

For more information, please contact Ronald Ullmann at syntrion@tiscali-dsl.de