Assault on the immune system

Kathryn NIXDORFF

The immune system plays a crucial role in protecting against infectious diseases, and the ability of a micro-organism to cause disease can only rightly be defined within the scope of its interaction with the immune system. To be a successful pathogen, a micro-organism must possess strategies that enable it to evade immune defence mechanisms. Immune responses are regulated to a great extent through the production of *cytokines*, bioregulators that can exert both positive and negative effects depending upon the amounts produced. The immune system is thus very vulnerable to malign use of both immune evasion strategies and immune bioregulators.

In this age of rapid biomedical and biotechnological advances, far-reaching manipulations of micro-organisms are now possible that can change their properties drastically. Experiments to manipulate micro-organisms are being carried out daily, with mostly peaceful aims in mind, such as the elucidation of the pathogenic mechanisms of an infectious agent, which could in turn point the way to the development of better prophylactic and therapeutic measures to counter infections more successfully.

However, it has become evident that these experiments can lead to the creation of particularly dangerous micro-organisms that can evade the immune responses in devastating ways. A prime example is the inadvertent creation of a killer mousepox virus by researchers trying to develop a virus-based contraceptive vaccine to control the rodent population in Australia.[1]

In addition to micro-organisms attacking the immune system, certain *biochemical agents* (substances produced by living organisms that act on biological systems but are chemical in nature) are also of particular concern. This represents a change of focus away from the possibility of using micro-organisms malignly *to cause infectious diseases* to the possibility of using biochemical agents *to disrupt the operation of biological systems*. It is also evident that with the rapid expansion of research activities in the areas of molecular biology and biotechnology, advances occur at an exponential rate—along with increasing capabilities for misuse.

In order to appreciate the dilemma of dual use and the possibilities of misuse in this area, a brief description of scientific and technological aspects underlying research activities in this field, including the elements of the innate and the adaptive immune systems, will be given. Because a successful pathogen has to be able to evade immune defence mechanisms, a few evasion mechanisms will be

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described before turning to an overview of the vulnerability of the immune system to modulation with bioregulators and targeted delivery systems, to modulation after immunization, and the potential for an assault on the immune system in interaction with the neuroendocrine system.

Structure and function of the immune system

The hallmark of the immune system is its ability to respond to an invasion of the body by micro-organisms or toxic components in ways that afford protection against detrimental effects that could occur. The responses of the immune system include both non-specific (innate immune system) and specific (adaptive immune system) components (see Table 1). These react in different ways to *antigens* (chemical components—mainly proteins and polysaccharides—of the micro-organisms), which are substances that can elicit an immune response if they are foreign to the host. Many antigens are not harmful by themselves, the exception being, of course, toxins. Micro-organisms are composed of a mosaic of many different antigens.

Antigens let the immune system detect what micro-organism is present, because there will be antigens that are very specific for a particular micro-organism. The immune system reacts to these antigens, mounting defence mechanisms that are designed to get rid of the micro-organisms. The non-pathogenic micro-organisms are removed readily, but the immune system must fight with pathogens and, as a result, initiate a response directed against those micro-organisms.

INNATE IMMUNE SYSTEM

The innate immune system represents the all-important first line of defence against pathogens and is absolutely essential for keeping an infection in check before adaptive immunity can be induced. If innate immunity is malignly attacked, the battle against infections is lost from the start.

The innate immune system includes components that are present and ready for action even before an antigen challenge is encountered. These cellular and molecular components are less specific than those of the adaptive system. That is, they are not specific for a particular antigen but react to classes of antigenic substances from micro-organisms called pathogen-associated molecular patterns (PAMPs). A simple analogy using car models and a specific manufacturer can be used to illustrate. All models of Volkswagen cars carry an identical VW emblem. A PAMP is like the emblem, which is present on all different models of Volkswagen vehicles. Any vehicle carrying this emblem would be recognized as manufactured by Volkswagen. However, this emblem provides no information as to the particular model of vehicle. This is very similar to the way in which the innate immune system recognizes many different micro-organisms carrying a particular PAMP as a class of micro-organism, but it is not able to identify the particular micro-organism. The adaptive immune system, on the other hand, is able to distinguish one particular micro-organism from another by recognizing other, more specific or distinctive, features of the model.

PAMPs are recognized by receptors on the cell's surface. Changing analogies, a PAMP could be considered as a key, and the receptor a lock. When a PAMP key fits a receptor lock, an immune response is "unlocked" within the cell.

Although several components of the innate immune system must be activated by activator substances (agonists) such as PAMPs in order to initiate an effective immune response, this activation can occur relatively rapidly, within minutes or hours.

The importance of innate immunity relative to the control over infectious diseases can be seen by the fact that the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health has expanded its programme significantly in order to attract immunologists to the area of biodefence research.[2] In this regard, NIAID reported that it "awarded a multi-component grant to create an 'encyclopedia' of innate immunity: a comprehensive and detailed picture of this ancient, essential first line of defense against bacterial and fungal diseases". The stated goal of this undertaking is to gain knowledge that could lead to the development of treatments for infectious diseases. At the same time, however, this information could provide a blueprint for malign attack of the innate immune system.

Adaptive immune responses

The cellular components of adaptive immunity (white bloods cells called *lymphocytes*) must be driven by antigens to go through different phases of activation, expansion (multiplication of cells) and differentiation in order to carry out their functions. Therefore, adaptive immune responses take days to activate, rather than the minutes or hours of an innate immune response. Additionally, adaptive immunity has a "memory" that allows a quicker and stronger response the next time that specific pathogen is encountered. Thus, adaptive immunity affords a high degree of specific protection, but it takes time to be induced.

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When receptors on the surface of a lymphocyte bind to specific antigens, this initiates a signal that is carried to the inner part of the cell, leading to its activation—which will enable it to carry out its function. The function of B lymphocytes is to produce antibodies while the function of T lymphocytes is to help regulate immune responses (in the case of T helper cells) or to initiate the death of infected cells (in the case of cytotoxic T cells).

The lymphocytes of adaptive immunity (B and T cells) are able to react to an antigen challenge with a high degree of specificity. As a result, immunity is afforded against one specific infectious agent carrying those antigens. However, B and T lymphocytes recognize antigens in different ways. B lymphocytes recognize the antigen itself, while T lymphocytes can only recognize an antigen when it

Table 1. Features of innate (non-specific) and adaptive (specific) immunity

Feature	Innate Immunity	Adaptive Immunity
Characteristics		
Specificity for micro-organisms	Relatively low (PAMPs)[a]	High (specific antigens)
Diversity	Limited	Large
Memory	No	Yes
Components		
Physical and chemical barriers	Skin, mucosal epithelia; anti-microbial chemicals, e.g. defensins	Cutaneous and mucosal immune systems; secreted antibodies
Blood proteins	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes (B cells that produce antibodies; T cells that carry out cell-mediated reactions)

Source: modified from A.K. Abbas, A.H. Lichtman and J.S. Pober, 1997, *Cellular and Molecular Immunology* (third ed.), Philadelphia, W.B. Saunders Company.
[a]PAMPs: pathogen-associated molecular patterns

is on the surface of another cell, bound to a specific molecule (known as a major histocompatibility complex, or MHC, molecule). MHC molecules serve an important function in the body as they allow the body to identify the difference between self and non-self. This self/non-self distinction that is dictated by MHC molecules determines to a great extent uniqueness at the cellular level. This is encountered when an organ from one individual is transplanted to another. The immune system identifies the MHC molecules of the transplanted organ as foreign and mounts a defensive response. If this natural response is not successfully suppressed though medication, it can lead to rejection of the transplanted organ. Only when the MHC molecules between donor and recipient are identical (i.e. self, as in the case of identical twins) will the immune system not respond.

However, when self MHC molecules present foreign antigens (such as antigens from a virus that has infected a cell of the body) to cytotoxic T lymphocytes, these respond with a reaction leading to the death of that virus-infected cell. In this way, the cell that was infected with the virus can no longer serve as a factory for producing more virus particles. Thus, T lymphocytes recognize that the MHC molecules are self, but what is attached to them (in this case, a foreign antigen) isn't.

Macrophages

Macrophages are a type of white blood cell that devours foreign antigens and invading microbes and then assists T lymphocytes in recognizing and reacting against cells that have been invaded by pathogens. They occupy a central position in the immune system, being active both in innate and adaptive immune responses.

In innate immunity, macrophages are activated through engagement of receptors on the cell surface by substances called agonists. Most prominent among receptors on the macrophage surface are the Toll-like receptors (TLRs), which bind PAMPs. The binding of a PAMP (agonist) to a TLR activates the cell to produce *cytokines*.[3] Cytokines serve as messengers in the immune system; they facilitate communication among immune system cells and between immune system cells and the rest of the body. One type of cytokine is known as an *interferon*; interferons are essential for a successful defence against many viral infections. Macrophages are also potent producers of *proinflammatory cytokines,* which mediate reactions designed to fight infections.

When cytokines are produced in moderate amounts, they contribute greatly to defence mechanisms directed against pathogens and to the healing process in general. If they are produced in particularly large amounts or continually during chronic illnesses, this can lead to various disorders such as autoimmunity, coronary insufficiency, thrombus formation, hypoglycemia, and in some cases even to shock and death.[4] On the other hand, if their production is suppressed, protection against infections may be compromised. Therefore, the activities of cytokines are particularly vulnerable to malign modulation to induce hyper- or inhibiting responses that could have detrimental effects.

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Macrophages bridge innate and adaptive immunity. After they have devoured foreign antigens or microbes as part of their role in innate immunity, they assist B cells and T cells in adaptive responses by producing cytokines that regulate lymphocyte function or by presenting antigens bound on MHC molecules so that these antigens can be recognized by T cells. Furthermore, they increase other substances (called co-stimulatory molecules) on their cell surface that can generally enhance their interaction with T cells.

Immune evasion by micro-organisms

In order for a micro-organism to be pathogenic, it must have a mechanism that permits it to evade immune defences. There is a great deal of interest in studying these processes with the aim of developing means of countering evasion strategies, which would permit, for example, the development of vaccines that defeat the evasion tactics of antigenic variation used by micro-organisms. At the same time, exploitation of evasion strategies with malign intent should be of particular concern. Some evasion strategies are described below.

Antigenic variation or mutation

Some micro-organisms frequently mutate or vary their antigenic composition so that they can no longer be recognized by the antigen receptors of immune system cells. With regard to particular antigens, some micro-organisms exhibit a much higher mutation rate than is normal. This is encountered, for example, in connection with the flu virus and HIV. This is one reason these infectious diseases are resistant to vaccination. In addition, some micro-organisms are subject to mutation due to pressures exerted by the immune system itself. Ironically, when the immune system reacts to a micro-organism, it is, in effect, encouraging the micro-organism to mutate.[5] In this regard, those antigens that elicit the strongest immune response will be subject to the greatest immune selection pressures.

Regulation of complement activity

One of the most important components of immunity is the *complement system*. This is some thirty or so substances in blood serum that become activated in a series of reactions during an immune response (known as a "complement cascade"). This process can be activated by microbial substances during innate immune responses, but also by antibodies in adaptive responses.

This is a further example of the importance of system balance. Insufficiencies in key components of complement would result in a devastating outcome with regard to certain infectious diseases, despite the use of antibiotics or other chemotherapeutic agents. On the other hand, unrestrained complement activation would cause severe damage to bystander cells. In a healthy body, complement activity is held in check by a variety of regulatory factors, known as regulators of complement activation (RCA).[6]

Members of the poxvirus, herpesvirus and retrovirus families produce homologues that mimic RCA proteins and are thus able to escape complement action.[7] The smallpox virus *Variola major* causes a serious, virulent infection in humans, while the virus that is used for vaccination against smallpox, vaccinia virus, usually causes only a very mild or even unapparent infection, at least in individuals with an intact immune system.

A component of the smallpox virus that may contribute to its pathogenicity (ability to cause disease) is the smallpox inhibitor of complement enzymes (SPICE). SPICE has the ability to inactivate one of the key complement components (human C3b) that serves to induce the innate immune process by which cells engulf material which is eventually digested, destroyed or killed. By inactivating the complement activity, a vital area of innate immunity would be disabled. Vaccinia virus also has a complement regulatory protein (called vaccinia virus complement control protein, VCP), which is, however, much less effective (100-fold less) than SPICE. In a recent report,[8] researchers mutated the

VCP gene of vaccinia virus to have the same nucleotide sequence as SPICE. The recombinant mutant VCP proved to be much more efficient than normal VCP in inactivating complement in a test tube reaction. Although the researchers did not actually outfit vaccinia virus with this mutated gene, the work was only one step away from this manipulation. Presumably, vaccinia virus with the mutated gene would be much more pathogenic.

Regulation of cytokine activity

As previously mentioned, interferons are cytokines produced by cells to protect them from viral infection, and anti-interferon strategies are a part of the immune evasion repertoire of most viruses. These mechanisms include the production of soluble versions of interferon receptors, which act as decoys. These decoys bind and inactivate interferons before they reach their "destination"—normal, membrane-bound receptors.[9]

Other cytokines, such as proinflammatory cytokines, are essential in directing the activities of different arms of the immune system. One of the most interesting evasion mechanisms identified in recent years is the mimicry of cytokines and cytokine receptors by large DNA viruses (herpesviruses and poxviruses). Cytokine homologues might redirect the immune response for the benefit of the virus, for example by suppressing the anti-viral activity of cytotoxic T cells. Alternatively, viruses that infect immune cells might use these homologues to induce signalling pathways in the infected cell that promote virus replication.[10] Furthermore, soluble cytokine receptors made by the virus might neutralize cytokine activity before the cytokines could react with their normal, membrane-bound receptors.

Inhibiting programmed cell death

A further immune evasion strategy includes the production of a variety of viral inhibitors of cell death (apoptosis), the so-called programmed cell death. In this regard, apoptosis can be viewed as a response to limit the intracellular propagation of viruses. The immune system recognizes a cell that has been infected by a virus through the presentation by that cell of fragments of viral proteins bound to MHC molecules on the surface of the cell. As stated above, unlike a B lymphocyte, a T lymphocyte will only recognize a virus that is attached to a MHC molecule. This recognition leads to the activation of cytotoxic T lymphocytes, which attack and kill the cell through the induction of apoptosis.

Some viruses can cause the suppression of the production of MHC molecules. This would mean that viral antigens would not be bound to MHC molecules and could not be recognized by T cells. The cell and therefore the virus production factory would be protected from cytotoxic T lymphocyte destruction.[11] Alternatively, viruses such as cytomegalovirus induce the expression of a certain type of MHC molecule that can bind a receptor on the surface of natural killer cells, inducing suppression of the activity of these cells that are normally an important component of innate immunity.[12]

Vulnerability of the immune system to modulation with bioregulators

In addition to immune evasion by pathogens, there has to be a great deal of concern about the possibility of modulating immune responses in a negative way with bioregulators that are not micro-organisms, but rather substances found normally in the body that regulate biological processes.

The inappropriate production of proinflammatory cytokines can be taken as an example of malign use of bioregulators. Enhancing the proinflammatory cytokine production by using PAMPs to engage Toll-like receptors on the surface of macrophages could at the very least lead to sickness behaviour, which is characterized by fever, drowsiness, lethargy and loss of appetite (normally signs that the immune system is "kicking in").[13] However, if the proinflammatory cytokines are produced in particularly large amounts, this could lead to autoimmunity, or eventually even to shock and death.[14] On the other hand, inhibiting the production of these cytokines by using bioregulators that can negatively regulate their synthesis might result in a lack of innate immune protection.

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A second example of modulation of immune responses with bioregulators concerns "super-antigens". The immune system is particularly vulnerable to attack by certain super-antigens. Normally, less than 0.01% of B or T lymphocytes respond to a particular antigen. In contrast, a number of super-antigens has been described that can react with a significant proportion of T lymphocytes (between 5–25%).[15]

For example, the bacterial product *Staphylococcus* enterotoxin B (SEB) is a biological agent that also falls into the category of a potential chemical weapon. This toxin was on the US list of favoured anti-personnel agents as early as 1949[16] and was apparently weaponized by the US Army prior to the negotiation of the Biological and Toxins Weapons Convention (BTWC).[17] It has also been the subject of extensive research in the biomedical literature. SEB acts as a super-antigen in that it can activate a large proportion of T lymphocytes to produce excessive amounts of cytokines, which can cause systemic reactions including inflammation, fever, widespread blood clotting and shock.[18]

Recently, a B cell super-antigen has been described that can bind up to 50% of the B cell population, resulting in an increased rate of apoptosis (death) of the bound cells.[19] Researchers are engineering this B cell super-antigen to achieve higher binding affinities and different specificities in order to specifically target malignant B cell populations such as lymphoma and leukaemia; therefore it could be considered for therapeutic use.[20]

Targeted delivery systems

Targeted delivery systems are components that allow an activity to be targeted to a particular site in the body where that activity is desired. Targeted delivery systems have to be characterized as being strongly dual purpose. While they may be potentially very useful in vaccine and gene therapy, they can also serve as delivery vehicles for dangerous toxins or bioregulators.

One example of a targeted delivery system is a *virus that is used as a vector to transfect a foreign gene* into a cell for the purpose of immunization or for gene therapy. Infection with the virus would lead to the production of the substance encoded by that foreign gene, for example, a foreign antigen.

Vaccinia virus has been investigated for immunization purposes because of its general effectiveness as a vaccine and its large genome, which can carry several foreign antigen genes at once.[21] Alternatively, the development of viruses called adeno-associated viruses as vectors for gene delivery seems promising, as these viruses are defective by nature and have thus never been shown to have any pathogenic effects in humans.[22]

In any case, it is evident that cytokines can be delivered quite effectively by viruses engineered to carry the cytokine genes. In the mousepox experiment previously mentioned, introduction of the

gene for the cytokine interleukin 4 into an otherwise relatively harmless virus had the devastating effect of suppressing an essential arm of immunity, making that virus into a killer.[23] Conceivably, super-antigens as well as other toxins and regulators of complement activation might also be successfully delivered by this means.

Another prime example of a targeted delivery system is an *immunotoxin*. Immunotoxins are molecules that consist of a toxin molecule coupled to an antibody that can bind specific antigens on the surface of particular cells. Most toxin molecules have two parts: the toxic portion and a binding portion. In the case of immunotoxins, the part of the toxin molecule that can bind its usual target has been removed and replaced with an antibody molecule. This permits the antibody to dictate a new target and redirect the molecule. The toxins that have been used to produce immunotoxins include ricin, *Shigella* toxin and diphtheria toxin. Immunotoxins have, for example, been used in tumour therapy. The aim is to target the toxin activity to specified tumour cells in a tumour therapy protocol; in this case, the antibody specificity is directed against tumour cell antigens.[24] A number of clinical trials using immunotoxins have been completed, while others are still going on. To-date, results have been promising in leukaemia and lymphoma patients, but responses in patients with large tumours have been disappointing. In any case, it is conceivable that biologically active substances might be directed to particular targets in combination with an antibody molecule.

Alternatively, molecules can be engineered to contain the toxic portion of a toxin linked to an antigen specific for a particular cell receptor. This antigen would direct the toxin to cells having that receptor. Such engineered molecules are called *fusion proteins*.

Aerosolization of vectors carrying foreign genes could represent an effective delivery system, especially if the vector is a virulent micro-organism, as most infections begin at the mucosa. If the bioregulator is not a micro-organism, such as in the case of cytokines, super-antigens or immunotoxins, successful delivery by the aerosol route depends greatly upon the physical and chemical properties of that vector. The US Army has apparently investigated the absorption of endogenous bioregulators through the aerosol route. It has reported, for example, that the hormone insulin and the proinflammatory cytokine IL-1 were effective in aerosol form in basic pulmonary absorption studies.[25]

There are still many technical problems involved with the use of targeted delivery systems that would serve to limit their application. However, there is tremendous interest in developing these systems further for therapy purposes and we can expect great advances in this area in the near future. As our understanding grows concerning targeted delivery systems, so should our concern regarding their misuse.

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Vulnerability of the immune system to modulation after immunization

Activation of the immune system in response to an infection is a vital step in countering the threat posed by the causative agent. Nevertheless, activation of components of the immune system is invariably associated with the enhanced production or exposition of predictable markers that could serve as targets for the delivery of a biological weapon to those sites.

B and T lymphocytes are produced during development of the immune system and prior to encountering antigens to yield an enormous number of cell clones, each being able to respond to a particular antigen.[26] Initially, only a small subset of these clones is able to recognize any one antigen. As previously mentioned, normally less than 0.01% of B or T lymphocytes can recognize a particular antigen.[27] To generate effective immunity, these “resting” B cells and T cell clones must multiply in

response to an antigen challenge in order to amass the numbers required to counter an infection. Depending on the strength of the challenge and the type of antigen, the lymphocytes are activated and then driven to divide ten to twenty times before they cease proliferation and proceed into a phase of differentiation, after which they are able to execute their functions. This represents a considerable expansion of antigen-specific lymphocytes in response to immunization, especially when a vaccine is given in several doses over period of time.

These expanded clones of B and T lymphocytes carry receptors specific for a particular antigen and therefore have an enhanced vulnerability, for example, to being targeted with constructed toxins as discussed earlier. For delivery to B cells, a delivery system might be an engineered or constructed *fusion protein* consisting of the specific antigen (against which the B cells are directed) fused or linked to the toxic portion of a toxin molecule. However, since B cells release antibodies directed against the antigen, the construct might be neutralized and cleared by these antibodies before it could do much damage.

T cells might be a more vulnerable target, as they do not secrete their antigen receptors. However, the delivery system containing the toxin would have to be constructed in such a way as to include the specific foreign antigen fragment bound to the part of a MHC molecule that could be recognized by the T cell. This would be a tall order to achieve at present, particularly in view of the fact that T cells can recognize only self MHC molecules. Nevertheless, new studies are providing greater insight into the fine points of the recognition of antigens presented by MHC molecules to T cells[28] that could make this approach more cause for concern in the future.

In addition to the expansion of specific antigen receptors, immunization also increases the expression of other molecules on the surface of lymphocytes and macrophages. Because of this enhanced expression, these markers could make the cell more vulnerable to attack, for example with immunotoxins.

Assault on the immune system in interaction with the neuroendocrine system

In the preceding article in this issue of *Disarmament Forum* the possibility of the malign misuse of neuroscience was discussed. It is increasingly recognized that the immune system interacts intricately and extensively with the nervous and the endocrine systems. There is a fine network of checks and balances exerted on the operation of all three systems by the elements within them. The perturbation of one system will invariably affect the operation of the others. All three systems are interconnected through the hypothalamus-pituitary-adrenal (HPA) axis via cytokines, hormones, neurotransmitters, peptides and their receptors, and also through hardwiring of neural and lymphoid organs.[29]

To illustrate how one system can affect another, with possible detrimental effects on both, the interaction of bioregulators of the immune system (cytokines) and the neuroendocrine system (hormones and neurotransmitters) within the HPA axis will be taken as an example. First of all, we will take a look at what occurs normally during an infection. Proinflammatory cytokines are produced by cells of the immune system after contact with micro-organisms or their products.[30] These cytokines gain entry into circulation from sites of the immune response in tissues and organs. Normally, they are of sufficiently large size that would prevent them from passing the blood-brain barrier. However, an area of the hypothalamus (the part of the brain involved in the control of such diverse functions as eating, drinking, sleep, thermoregulation, cardiovascular regulation and hormone secretion) represents a window in the barrier, allowing the entry of the cytokines into this region.[31] They subsequently bind to receptors on cells in the hypothalamus and trigger reactions collectively known as sickness behaviour, which is characterized by fever, drowsiness, lethargy and loss of appetite.[32] In this way, the immune system is signalling the brain that rest is needed to help speed recovery.

However, if the reaction is too strong, it could be very debilitating. To keep the actions of the proinflammatory cytokines from getting out of hand, these same bioregulators have another effect on the hypothalamus, which is to induce the production of *corticotropin-releasing factor* (CRF).[33] This is a hormone that is involved in immune regulation. It causes the pituitary to produce adrenocorticotropic hormone (ACTH). This hormone enters the circulation and acts on the adrenal gland cortex to induce the production of glucocorticoids, which have a profound effect in suppressing immune responses, thus turning off the production of proinflammatory cytokines before they are overproduced.

Yet again, balance is key. CRF can have a potentially detrimental effect on the central nervous system if it is overproduced. CRF has been associated with major depression, anorexia nervosa and Alzheimer's disease.[34] Overproduction of CRF has also been implicated with damage to brain cells in animal studies. In these investigations, a stroke was induced in the animals. It could be shown that the damage to brain cells (neurons), which occurred as a result of the stroke, could be prevented, if certain specific substances inhibited the action of CRF. [35]

Normally, these interactions within the HPA axis work as a check and balance system to keep reactions from getting out of hand. However, it is easy to see that a selective overproduction of proinflammatory cytokines could tip the balance to enhance detrimental effects on both the immune and the neuroendocrine systems, leading to debilitating sickness behaviour, significant immune suppression and even damage to brain cells.

Conclusions

In this article, the dual-use dilemma of modern biotechnology has been viewed within a broader scope of consequences by focusing on biological systems as the target of potential malign intent, using the immune system as an example. The possibility of the perturbation of this system not only with micro-organisms designed to evade immune defences, but also with bioregulators that can profoundly affect its function, raises the dual-use dilemma to a higher order of concern. This becomes even more complex when interactions of such vital biological systems as the immune and neuroendocrine systems and their vulnerability to manipulation with bioregulators are considered.

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The overwhelmingly rapid advances in biotechnology are pitted against a Biological and Toxin Weapons Convention that has no treaty organization and inadequate mechanisms for verifying compliance. This situation highlights the need for additional control measures. Preventive arms control criteria emphasize the need for monitoring research to provide possible early warning of potentially dangerous developments. In this regard, serious consideration should be given to the improvement of research oversight, at the least as a contribution to raising awareness of the dual-use problem inherent in biomedical research in the scientific community.

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The on-going siege to which we are all subjected, 24/7/365, is unprecedented in our history. Yet, it is difficult for people to realize and â€œconnect the dotsâ€Â because: (1) so much of it is invisible and off our radar; (2) mainstream media is corporate-controlled disinformation; and (3) most Western physicians have not had any training in environmental medicine.Â When Big Pharma goes into the rain forest, poisons the rivers and harms the entire eco-system, to extract and synthesize some essential part of a medicinal plant, they remove the synergistic benefits accruing from the WHOLE plant. However, when one uses the entire plant, there is a marvelous and synergistic benefit happens that benefits healing. In multiple sclerosis, the immune system attacks 'self' tissues. Ten years after the discovery of one target of this autoimmunity, work with mice identifies it as a guardian protein produced in response to inflammation. | Never the twain shall meet.Â CRYAB-directed autoimmunity in demyelinating conditions (Ousman et al. 2007) has thus been termed an 'assault on the guardian', which can enhance inflammatory damage (Ransohoff 2007). Uncoupling of Neuroinflammation from Axonal Degeneration in Mice Lacking the Myelin Protein Tetraspanin-2. Article. Macrophages are cells of the immune system that protect the host from invading pathogens. But in cancer, macrophages can be "hijacked" by tumors, and made to support their malignant growth and spread. This is a drawback for a major cancer treatment, immunotherapy, which turns the body's immune system against the tumor. EPFL scientists, working with colleagues at the Roche Innovation Centers in Munich and Basel, have now identified a molecular "switch" that can convert the "hijacked" macrophages into cells that can stimulate the immune system to fight the grow