Interactions between Infections, Nutrients and Xenobiotics

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TemaNord 2005:538

© Nordic Council of Ministers, Copenhagen 2005

ISBN 92-893-1166-5

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The Nordic Food Policy Co-operation

The Nordic Committee of Senior Officials for Food Issues is concerned with basic Food Policy issues relating to food and nutrition, food toxicology and food microbiology, risk evaluation, food control and food legislation. The co-operation aims at protection of the health of the consumer, common utilisation of professional and administrative resources and at Nordic and international developments in this field.

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Preface

The Nordic Committee of Senior Officials for Food Issues is an advisory body of the Nordic Council of Ministers which co-ordinates Nordic work in the field of food and nutrition. The Committee has given the Nordic Working Group on Food Toxicology and Risk Evaluation (NNT) the responsibility to promote co-operation and co-ordination among Nordic countries on matters relating to food toxicology and risk assessment.

During recent years there has been several incidents of chemical substances that has contaminated food (e.g., TCDD), high levels of xenobiotics in food (e.g., mercury, TCDD), as well as outbreaks of infections in food producing animals (e.g., BSE and influenza in chicken). Consequently, interactions between infectious agents, nutrients, and xenobiotics has become a developing concern in food toxicology, as well as in food-born diseases in which xenobiotics may affect host resistance and micro-organism virulence.

The present report is a review of articles, published in scientific journals, that covers the area of interactions between infectious agents, nutrients, and xenobiotics. The intention was, when the project was initiated in 1999, to create a project group of scientifically skilled members from the Nordic countries that should cover the different scientific areas of the project. However, it was not possible to find expertise that could participate in the project group and the report has therefore, after critical reading by Göran Friman and thorough discussions within the NNT group, been finalised by the project leader Nils-Gunnar Ilbäck.

Summary

Interactions between infectious agents, nutrients, and xenobiotics is a developing concern in food safety, as well as in food-borne diseases in which xenobiotics may affect host resistance and microorganism virulence. The sum of all interactions at the host-pathogen interface, including initiation of the infectious process, propagation of the infectious process, and the mounting of a corresponding host immune response, ultimately determines the outcome of an infection. It is a delicate balance between the infected host and the microorganism, including their nutritional requirements, as well as competition between nutrients and xenobiotics, in both the host and the microorganism. Consequently, both the course of the disease and the toxicity of the xenobiotic could be influenced by how this pattern of interactions is balanced.

A few plausible explanations for the mechanisms underlying interactions between infections, nutrients, and xenobiotics are (a) the immune system is affected by the chemical substance in a way that it functions less effectively, resulting in decreased host resistance, (b) the gastrointestinal uptake, the tissue distribution, and metabolism of the chemical substance in the body are altered by the infection, such that the damage to the target organs of the chemical substance increase or even that new organs become the target for toxic insult, and (c) the chemical substance itself affects, alternatively changes, the environment of essential nutrients in such a way that the microorganisms multiply in increasing numbers or that more aggressive mutants get the opportunity to predominate.

An increased health hazard by chemical substances in association with infections can thus be explained in part by changed disease pathogenesis that is caused by the redistribution and accumulation of chemical substances occurring in the organs of the body involved in the infection, and, in part, by a possibly changed virulence of microorganisms in target organs of infection. Some chemical substances clearly increase the susceptibility to infectious microorganisms, change the course of the infection and the virulence of the microorganism, resulting in a more severe disease, as well as reactivate resting organisms that normally are present in the body after a primary infection. Even low-dose exposure to xenobiotics without any clinical signs of toxicity or significant immune effects when tested in vitro seems to have the capability to jeopardise the host defence in vivo to a variety of microorganisms. Consequently, infections may well have an impact on the toxicity of xenobiotics, unfolding the possibility for detrimental effects even at exposure levels normally regarded as safe.

In addition, the host nutritional status is crucial for the host defence and the outcome of the disease, as well as for the handling and detoxification of hazardous chemical substances in infection. Hitherto studied chemical substances in infection many times show changed and substance-specific distribution, and for some chemical substances there is even accumulation in new target organs involved by the disease. An infection-induced decrease in detoxification increases the body burden of xenobiotics and many times the severity of the disease. In addition, infections are associated with changes in essential trace elements that may cause an unfavourable deficiency of essential trace elements in target organs of infection and xenobiotic accumulation. This may affect the growth of a pathogen, increase microorganism virulence, and disturb the healing of infection-induced inflammatory lesions. Storage of potential immunotoxic substances in target tissues of infection and inflammation can therefore generally be assumed to carry an increased risk of having a negative impact on the disease process. With an increasing number of emerging pathogens and the increasing resistance of important pathogens to available antibiotics and other medications, nutrients and chemicals are likely to receive increased future attention. Accordingly, there is an urgent need for knowledge how non-essential and potentially toxic elements interact with essential nutrients in common infections.

It seems therefore that even normal and harmless amounts of xenobiotics can constitute a health hazard if, at the time of exposure, the individual carries or is exposed to infection. Because each individual is typically exposed to a large number of infections, we can count on the fact that during an individual's lifetime, different vital organs will be "occasional target organs" a considerable number of times for potentially different harmful chemical substances. What role these "multiple hits" of infections on different organs play in the long run for organ function and the individual's health remains to be solved. Furthermore, xenobiotics accumulated during the lifetime of the individual may pose an unrecognised hazard because of the redistribution from depot tissues to sensitive organs that seems to occur for several substances during common infections.

Therefore, from a health perspective, in the risk assessment of xenobiotics in our food and environment we need to include synergistic effects between microorganisms, nutrients, and xenobiotics. We should further consider that an unfavourable interaction between infections, nutrients, and xenobiotics in the food and environment may gradually change the illness panorama. The report is a review of specific scientific studies illustrating the points addressed in general in the summary.

Abbreviations

Ah-R	arylhydrocarbon receptor
As	arsenic
B. abortus	Brucella abortus (bacteria)
CBV	coxsackievirus
Ca	calcium
C. albicans	Candida albicans (fungi)
CBV	coxsackievirus, type B
Cd	cadmium
CMV	cytomegalovirus
C. pneumoniae	Chlamydia pneumoniae (bacteria)
Co	cobalt
Cu	copper
CYP450	cytochrome P450 enzymes
E. coli	Escherichia coli (bacteria)
EMCV	encephalomyocarditis virus
Fe	iron
HCB	hexachlorobensen
Hg	mercury
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IFN	interferon (cytokine)
IL	interleukin (cytokine)
K. aerogenes	Klebsiella aerogenes (bacteria)
L. major	Leishmania major (parasite)
L. monocytogenes	Listeria monocytogenes (bacteria)
Mg	magnesium
Mn	manganese
MT	metallothionein
M. avis	Mycobacterium avis (bacteria)
M. tuberculosis	Mycobacterium tuberculosis (bacteria)
Ni	nickel
NK cell	natural killer cell
Pb	lead
PBDE	pentabromodiphenyl ether
PCB	polychlorinated biphenyl
P. berghei	Plasmodium berghei (parasite, malaria)
PRV	pseudorabies virus
mRNA	messenger ribonucleic acid
Se	selenium
SFV	semliki forest virus

SLEV	St. Louis encephalitis virus
S. aureus	Staphylococcus aureus (bacteria)
S. enteritidis	Salmonella enteritidis (bacteria)
S. pneumoniae	Streptococcus pneumoniae (bacteria)
S. typhimurium	Salmonella typhimurium (bacteria)
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
T. cruzi	Trypanosoma cruzi (parasite)
T. lewisi	Trypanosoma lewisi (parasite)
T. musculi	Trypanosoma musculi (parasite)
T. spiralis	Trichinella spiralis (parasite)
TNF	tumour necrosis factor (cytokine)
VEEV	Venezuelan equine encephalitis virus
Zn	zinc

1. Introduction

Interactions between infectious agents, nutrients, and xenobiotics is a developing concern in food safety, as well as in food-borne diseases in which xenobiotics may affect host resistance and microorganism virulence. These interactions include a delicate balance between the infected host and the microorganism, including their nutritional requirements, as well as competition between nutrients and xenobiotics, in both the host and the microorganism (Fig 1). Consequently, both the course of the disease and the toxicity of the xenobiotic could be influenced by how this pattern of interactions is balanced.

Every year, in the U.S. and Western Europe food-borne infections cause millions of illnesses and thousands of deaths, although most infections go undiagnosed and unreported (McDade, 1997). Occurrence of disease is a function of several variables, the virulence of the microorganism, its mode of transmission, and host susceptibility. A theory has also been advanced that certain new “emerging” infections may reflect a more contaminated environment and a changed nutritional status of the population (Gauntt and Tracy, 1995; McDade, 1997). Enhanced mortality of animals exposed to xenobiotics has been noted in viral, bacterial, and parasitic infections. However, only a few studies have been performed that describe infectious complications in humans after exposure to environmental chemicals. For example, an increased incidence of common cold and influenza in Pb-exposed workers (Ewers et al., 1982) and of malaria in Hg-exposed workers (Crompton et al., 2002), has been reported. Respiratory infections were also more frequently found in humans accidentally exposed to PCB than in non-exposed individuals (Shigematsu et al., 1978), whereas such a difference could not be confirmed in humans exposed to TCDD (Evans et al., 1988). Recently, it was reported that a higher postnatal PCB exposure among healthy Dutch preschool children was associated with a higher prevalence of recurrent middle ear infections and chicken pox (Weisglas-Kuperus et al., 2004).

Figur 1. Potential interactions between infection, nutrients and xenobiotics. Interactions include a delicate balance between the infected host and the microorganism, including their nutritional requirements, as well as competition between nutrients and xenobiotics, both in the host and the microorganism

In addition to a variety of potentially harmful xenobiotics, we are constantly exposed to a number of different, potentially contagious infectious agents from the environment and the food we consume. Viruses are increasingly noted as important causes of food-born disease (McDade, 1997). Some infections are successfully controlled through medical treatment, whereas others have decreased in frequency because of increased hygienic standards, vaccination programmes, etc. However, infections are still common in our societies and new "emerging" infections appear at regular intervals worldwide (McDade, 1997). SARS is the latest in a series of new infectious diseases (e.g., HIV/AIDS, Ebola, Nipah, and avian H5N1 influenza) that are adding additional stress to our healthcare system. In addition to the number of newly discovered infections, old pathogens with new properties ("re-emerging" infections) have increased in recent years. One example is the "urban trench fever" striking homeless and alcoholic men in France, the U.S., and Finland as reported in 1995 (Drancourt et al., 1995; Spach et al., 1995). The causative bacteria are of the same species as those giving rise to trench fever during the two world wars. Furthermore, "old" diseases, long thought to be non-infectious, have recently been found to have an infectious etiology, including gastric and duodenal ulcer caused by *Helicobacter pylori* (Blaser, 1990). Because microorganisms adapt to changes in the surroundings more quickly than people (McDade, 1997), it cannot be ruled out that, in addition to weakening the host defence, a more contaminated environment may promote the development of pathogens in an unfavourable direction (Fig.1). One specific example of adaptation of great concern in health care is the emergence of resistant bacteria resulting from the liberal use of antibiotics in many countries.

There are common microorganisms, to which all humans are repeatedly exposed during their lifetime, such as viruses and bacteria causing respiratory infections. Generally, respiratory infections are among the most common of all infections and each individual suffers a great number of such infections during the course of his or her life. Adults and children in the United States experience from two to six colds per year (Prasad et al., 2,000). In temperate zones the common cold viruses predominate, whereas in tropical zones various other respiratory viruses and bacteria cause high morbidity and mortality, particularly in underprivileged children. *Chlamydia pneumoniae* is a recently identified bacterium causing upper respiratory disease at a high frequency worldwide with cyclic variation over time (Nystrom-Rosander et al., 2003). Approximately 70% of elderly people in temperate as well as tropical zones have antibodies to *C. pneumoniae* as a marker of previous infection with that bacterium (Nystrom-Rosander et al., 2002). Although most respiratory infections cause only mild to moderate symptoms in a majority of cases, they sometimes give rise to aggravated disease as well as complications, such as pneumonia, myocarditis, pancreatitis, meningoencephalitis, and even atherosclerotic lesions (Ilback et al., 1990; Nystrom-Rosander et al., 2003; Woodruff, 1980).

Depending on host resistance, several infections can develop in different directions (symptomless/subclinical infection, acute clinical disease, or chronic infection), resulting in complete recovery or various complications (Table 1). For most microorganisms, symptomless or subclinical infection is the most common situation. Thus, we are often infected but

Table 1. Potential results of virus - host interactions

Interaction	Result
Host is resistant	No infection established
Subclinical infection	Complete recovery
	Persistent or latent infection
Acute clinical disease	Death
	Complete recovery
	Recovery with persistent or latent infection
Chronic infection	Asymptomatic with latent virus
	Latent with recurrence
	Persistent - chronic infection
	Malignant transformation

our host defence, in most instances, protects us from developing any clinical illness. However, with a high enough dose of microorganisms, in combination with insufficient immunity to that particular organism, individuals with otherwise normal immune function will develop disease. Individuals with a suppressed immune function pose a particular problem. It is apparent from a number of clinical studies that suppression of the immune system (e.g., as a result of pharmacotherapy following organ transplantation) is characteristically associated with increased susceptibility to different infectious diseases as well as an aggravated clinical course

once disease develops. Thus, increased sensitivity to infections and a serious course of normally mild infections indicate a failing immune defence. Moreover, an increasing number of reports suggest that nutritional imbalances caused by certain chemical substances in the food and environment can likely weaken the immune function in otherwise healthy individuals. For instance, Hg and Cd, even in the relatively low concentrations that are present in our food can disturb the functioning of certain arms of the immune system that are important in our host defence to invading pathogens (Burchiel, 1999; Lawrence et al., 2000).

In developing countries and poor communities micronutrient deficiencies and infectious diseases often coexist and exhibit complex interactions, many times resulting in severe complications. From epidemiological studies, it is well known that malnourished children develop a greater severity of measles and many other infections (Beisel, 1991; Bhaskaram, 2002). Interestingly, studies of Zn supplementation on infectious disease and mortality in the developing world showed reduced incidence of clinically diagnosed pneumonia and possibly also on the incidence of malaria (Black, 2003). The combined effect of nutritional deficiencies and exposure to low concentrations of xenobiotics can therefore be assumed to adversely interact in our defence against infections and constitute a potentially increased health risk.

A few early experimental studies during the 1970s-80s showed increased lethality in infected individuals when exposed to immunotoxic chemicals (Friend and Trainer, 1970; Imanishi et al., 1980; Thigpen et al., 1975) or when fed a nutritionally deficient diet (Woodruff, 1970; Woodruff and Kilbourne, 1970). However, there were some discrepancies between studies. For example, two studies reported the resistance to the gram positive bacterium *L. monocytogenes* to be intact after TCDD exposure (House et al., 1990; Vos et al., 1978), whereas two other studies showed host resistance to be compromised (Hinsdill et al., 1980; Luster et al., 1980). Part of the explanation to conflicting results in these and other early studies may be attributable to different experimental conditions in terms of animal strain and species, type and strain of microorganism, dose and route of administration, and test substance regimen.

Variability in host sensitivity and disease development also seems to depend on in which phase of the disease the toxic test substance has been administered before infection, during the incubation period, the acute illness of the disease, or during the convalescent period (Fig. 3). With these contradictory results in mind, it is not surprising that only few human studies have been able to show a clear link between infectious complications and exposure to immunosuppressive environmental chemicals (Descotes and Vial, 1994). Notwithstanding, as suggested by many experimental studies, it seems highly plausible that increased susceptibility to infections and proneness to develop subsequent complications can be

influenced by environmental toxicants, even in humans, and is thus not fully explained by “lack of nourishment” or “innate predisposition”.

Twenty-five years ago Loose et al (Loose et al., 1978) found that mice infected with malaria (*P. berghei*) and exposed to PCB and HCB had higher contents of these xenobiotics in their lymphoreticular organs than had non-infected mice exposed to similar amounts of these toxicants. Moreover, about 10 years ago it was shown for the first time that a common viral infection (CBV) could change the distribution in the body of Cd (Ilback et al., 1992b) and Ni (Ilback et al., 1992a), but with a different organ distribution pattern for these two metals. A few years after this finding Luebke et al (Luebke et al., 1994) suggested, using a parasite infection, that TCDD elimination is delayed during infections. Concomitantly, it was shown that a virus infection could increase the uptake of TCDD in the target organs of the infection (Funseth and Ilback, 1994). These and other data raise concern that the toxicity of chemicals may increase when exposure occurs during ongoing infection.

From the above findings, the hypothesis has developed that an interaction between infections, nutrients and potentially harmful chemical substances in food and in the environment can result in a changed illness panorama. One example is the supposition that PCB- and TCDD-related substances (halogenated aromatic hydrocarbons) were the cause of the high death rate that appeared in the early 1990s among morbillivirus-infected seals living in the contaminated waters around Scandinavia (Ross et al., 1996; Van Loveren et al., 2000) and in harbour porpoises from England and Wales (Jepson et al., 1999). Other examples are early studies using lymphocytic choriomeningitis virus (LCMV) in mice suggesting that cumulative environmental insults from chemicals can potentiate a persistent virus to induce diabetes (Tishon and Oldstone, 1987; Toniolo et al., 1980).

Whether in experimental or epidemiological studies, toxic effects of xenobiotics in infections are difficult to evaluate because they influence many mechanisms and responses used by the body to defend itself against the invading microorganism. These several lines of host defence are complex and involve a number of physiological, biochemical, immunological, metabolic, and hormonal mechanisms (Beisel, 1998; Friman and Ilback, 1998; Grimble, 1996; Powanda and Beisel, 2003). Thus, well-designed experimental studies are needed to pin down effects on each defence mechanism, as well as to clarify the complicated interactions that potentially can occur between microorganisms, nutrients, and chemical substances.

2. Infections and Models Used in Host Resistance Studies

Following infection, microorganisms must battle against the host's defence, where either the host eliminates them or they eliminate the host. The ability of a pathogen to cause infection depends on a successful colonisation of the host, which, in turn, requires the adaptation to various defence mechanisms presented by the host (Table 2). As a response to acute infections, the host evokes a multitude of responses some of which are stereotypic and similar in various infections and occur as a systemic acute phase reaction to the invading microorganisms (see "the acute phase reaction") (Fig. 3), whereas others are specific to the causative microorganism (Beisel, 1998). Thus, in viral, bacterial, fungal, protozoan, and helminth infections humoral and/or cell-mediated arms of the immune system are variably activated and directed to different organism-specific epitopes. For example, many viral infections, including the CBV infections, are characterized by the formation of virus-neutralising antibodies with the function of limiting the spread of the infection, as well as activation of virus-specific cytotoxic and cytolytic T-cells, which function to limit the production of new virus particles in infected target cells (Modlin, 1995). However, viruses have developed many ways to escape immune surveillance and down-regulate the host's immune response (Naniche and Oldstone, 2000). For instance, measles virus, HIV, and CMV are all known to cause immunosuppression. In some viral infections the infected cells undergo apoptosis before viral replication, which may be a cellular defence mechanism to prevent viral propagation, whereas other viruses gain advantage by preventing apoptosis by producing proteins that inhibit apoptosis (Fernandez-Pol et al., 2001). The host response to viral infections also involves a scavenger function, i.e. specific immune cells remove debris from the infected tissues, and reparative mechanisms and healing of lesions in target organs of infection are subsequently initiated. Cellular inflammatory responses to infections are therefore part of the host defence against invading microorganisms.

Table 2. Host defence mechanisms against infectious agents

External defences	Skin, mucosal lining of the respiratory, gastrointestinal, and urogenital tracts	
Natural immunity	<u>Cells:</u>	phagocytes, natural killer cells, and mast cells
	<u>Molecules:</u>	complement, interferons, acute-phase reactants, lysozyme, and defensins
Adaptive immunity	<u>Cells:</u>	T and B cells, antigen presenting cells (T and B cells, and macrophages)
	<u>Molecules:</u>	immunoglobulins
General adaptation	Fever, anorexia, somnolence, changed gastrointestinal uptake, endocrine, and metabolic responses	

A qualitative and quantitative prediction of the effects of nutrients and chemicals on the host defence requires relevant experimental infection models. Experimental studies should as accurately as possible reflect the disease in humans. Furthermore, diseases that are common in the population have priority. Accordingly, for each chemical substance under study, an optimal animal model should use a microorganism causing a similar course of disease, immune responses, and pathogenesis as in humans. This allows for a mechanistic investigation of immunological defects responsible for a modified host resistance. Moreover, the model must enable a quantitative and qualitative measurement of endpoints that reflect the severity of the disease. This is a key issue in the evaluation of the influence of various compounds on host resistance. Different animal infection models using viruses, bacteria, and various parasites have been developed for such studies (Table 3).

People are repeatedly exposed to certain common viruses throughout their life, such as influenza viruses (respiratory infection), and the enterovirus CBV (infection primarily in the gastrointestinal tract). The enterovirus family includes about 70 viruses. They are divided into the Coxsackie A and B viruses, the polioviruses, and the echoviruses (Modlin, 1995). During infection, the virus binds to cell receptors and is taken up in the host cells where it yields its single-stranded RNA that directly functions as mRNA. The virus genome (RNA) codes for structural proteins and proteins necessary for virus replication.

Normally, enterovirus infections pass unnoticed or cause only mild symptoms in the upper respiratory system or in the gastrointestinal tract. However, especially the polioviruses are prone to cause severe disease of the central nervous system, in several cases resulting in palsy or death. Even in several cases of coxsackie and echovirus infection complications develop, including myocarditis, pancreatitis and meningoencephalitis (Ilback et al., 1989; Ilback et al., 2003a; Ilback et al., 2005a,b; Modlin, 1995; Woodruff, 1980).

Well characterised experimental mouse models are available for studies of CBV infection, showing a disease development that is very similar to that in humans (Fohlman et al., 1990a; Ilback et al., 1990; Woodruff 1980). In these models it has been demonstrated that human pharmaceutical drugs (Fohlman et al., 1996; Ilback et al., 1993b; Kyto et al., 2002) and experimental vaccines have a protective effect (Fohlman et al.,

1990b). CBV models have also been used in studies of interactions between infection, nutrients, and potentially harmful chemical compounds, including Cd, Hg, Ni, Acrylamide, PBDE, and TCDD. The CBV infection models are the most commonly used experimental infection models in this area of research (see ADME studies, Table 3).

Table 3. Host resistance models in rats and mice used for studies of xenobiotics and nutrients.

Microorganism	Chem./nutrient	Target effect of chem./nutrient treatment	Reference
<i>Bacteria</i>			
<i>E. coli</i>	Bisphenol A	↓ bacterial clearance, phagocytic activity, IL-6, immune cells	Sugita-Konishi et al. 2003b
<i>L. monocytogenes</i>	Cd	↑ mortality	Simonyte et al., 2003
<i>L. monocytogenes</i>	Pb	↑ sickness behaviour, ↓ T helper/cytotoxic cells	Dyatlov and Lawrence, 2002
<i>L. monocytogenes</i>	Pb	↑ mortality	Hinsdill et al., 1980
<i>L. monocytogenes</i>	TBTO	↓ NK cell activity, macrophage function, clearance of bacteria	Vos et al., 1990
<i>L. monocytogenes</i>	TCDD	↔ mortality	Luster et al., 1980
<i>L. monocytogenes</i>	TCDD	↔ mortality	House et al., 1990
<i>L. monocytogenes</i>	TCDD	↔ bacterial clearance	Vos et al., 1978
<i>L. monocytogenes</i>	TCDD	↓ bacterial clearance, ↑ TNF, IFN, ↔ immune parameters	Sugita-Konishi et al., 2003a
<i>M. tuberculosis</i>	Fe	↑ no. bacteria in spleen and lungs	Lounis et al., 2001
<i>Salmonella bern</i>	TCDD	↑ mortality	Thigpen et al., 1975
<i>S. typhimurium</i>	Pb	↑ mortality	Hemphill et al., 1971
<i>S. typhimurium</i>	Pb	↑ mortality	Hinsdill et al., 1980
<i>S. aureus</i>	As and Pb	↓ bacterial clearance, macrophage migration	Bishayi and Sequpta 2003
<i>S. aureus</i>	Se deficiency	↔ mortality, bacterial clearance	Boyne et al., 1986
<i>S. pneumoniae</i>	Zn deficiency	↓ survival time, ↑ early onset of bacteria in blood	Strand et al., 2001
<i>S. pneumoniae</i>	Zn deficiency	↑ no. of bacteria in lung, mortality, severity of infection	Strand et al., 2003

Microorganism	Chem./nutrient	Target effect of chem./ nutrient treatment	Reference
<i>Virus</i>			
CBV	Se-deficiency	↑ virulence, inflammatory Lesions	Beck et al., 1994
CBV	Se suppl	↑ survival, T-killer/ helper cells-macrophages in tissue lesions	Ilbäck et al., 1989
CBV	Se suppl	↑ survival, (↑) T helper/cytotoxic cells, NK cell activity in blood	Ilback et al., 1998
CBV	Cholesterol	↑ lipid accu, macrophages, ↔ T-killer/helper cells in inflammation	Ilback et al., 1990
CBV	Cholesterol	↑ fatty metamorphosis in liver, ↓ virus	Loria et al., 1976
CBV	TCDD	↑ uptake in brain, pancreas, heart, liver, spleen	Funseth and Ilback, 1994
CBV	TCDD	Redistribution to thymus and brain	Funseth et al., 2002c
CBV	TCDD	↓ P450, ↑ MT, IFN	Funseth et al., 2002a
CBV	TCDD	↓ inflammatory lesions, (↓) virus. Changed trace element balance	Funseth et al. 2002b
CBV	Cd	↑ B cell activity, ↓ no. T and B cells in inflammatory lesions	Ilback et al., 1994b
CBV	Cd	↑ dose-dependent G.I uptake in body, liver, kidney, heart	Glynn et al., 1998
CBV	Cd	↑ uptake in renal and adrenal cortices	Ilback et al., 1992b
CBV	Cd	↑ Fe accumulation in brain as focal deposits	Ilbäck et al., 2005b
CBV	Ni	↑ uptake in pancreas, heart	Ilback et al., 1992a
CBV	Ni	↑ inflam./necrotic lesions, ↓ T-killer/helper cells- macrophages	Ilback et al., 1994a
CBV	Hg	↑ inflam./necrotic lesions macrophages, (↑) IFN, virus	Ilback et al., 1996
CBV	Hg	↑ Ca, Mn, Fe in inflam./ necrotic lesions, ↓ Zn	Ilback et al., 2000
CBV	PBDE	↑ uptake in liver, lungs, pancreas, ↓ EROD, PROD	Darnerud et al., 2005
CBV	Acrylamide	↑ blood, thymus, ↓ pancreas	Abramsson-Zet- terberg et al., 2005
CMV	Ni	↑ mortality, ↓ NK activity, ↔ IFN	Daniels et al., 1987
CMV	Cd	↔ mortality, IFN, ↓ NK activity	Daniels et al., 1987
EMCV	DDT, fenitrothion	↑ mortality	Crocker et al., 1974
EMCV	Parathion	↑ mortality, ↓ P450	Selgrade et al., 1984
EMCV	Cd	↓ mortality,	Exon et al., 1979
EMCV	Pb	↑ mortality	Exon et al., 1979

Microorganism	Chem./nutrient	Target effect of chem./ nutrient treatment	Reference
EMCV	Co	↑ virus, mortality, tissue accumulation	Gainer, 1972
EMCV	As	↓ mortality (prior exp.), ↑ mortality (exp. during infection)	Gainer and Pry, 1972
EMCV	Hg	↑ mortality, ↔ Hg in kidney	Koller, 1975
EMCV	Pb, Hg, Ni	↑ mortality	Gainer, 1977
EMCV	Cd, Mn	↑ mortality, brain tissue pathology, early onset of virus in brain	Seth et al., 2003
HSV	Hg	↑ Hg in macrophages, ↔ virus, IFN, TNF	Christensen et al., 1996
HSV	Hg	↑ virus	Ellermann-Eriksen et al., 1994
HSV	Cd	↓ T and B cell activity, ↔ mortality, ↑ tissue accumulation	Thomas et al., 1985
HSV	Cd	Reactivation of virus	Fawl et al., 1996
HSV	PCB	↑ mortality, accumulation in liver, ↔ IFN	Imanishi et al., 1980
PRV (Herpesvirus)	TCDD	↑ mortality	Thigpen et al., 1975
Influenza	Se-deficiency	↑ virulence, lung pathology	Beck et al., 2001
Influenza	TCDD	↑ mortality	House et al., 1990
Influenza	TCDD	↑ mortality, ↔ virus, thymus weight	Burleson et al., 1996
Influenza	TCDD	↔ mortality	Nohara et al., 2002
Influenza	TCDD	↑ pulmonary inflammation, mortality, ↔ virus	Luebke et al., 2002
Influenza	TCDD	↓ no. of virus-specific cytotoxic T lymphocytes	Mitchell and Lawrence, 2003a
Influenza	TCDD	↑ neutrophils/inflammation in lung, ↔ IFN, IL-12, T cells, ↓ IgG	Vorderstrasse et al., 2003
Influenza	TCDD	↓ T-cell dependent functions in lung, ↑ IFN in lung	Warren et al., 2000
Influenza	TCDD	↓ immune memory response, ↔ host resistance in re-infection	Lawrence and Vorderstrasse, 2004
Influenza	TCDD	↑ mortality, neutrophilia	Teske et al., 2005
Influenza	Cd	↑ phagocytic cells in lung, ↔ IFN, antibodies	Chaumard et al., 1991
Influenza	Toximul (surfact)	↑ mortality, liver effects, changes in urea cycle	Crocker et al., 1986
SFV	Pb	↑ mortality, virus	Gupta et al., 2002
SFV	Cd, Mn	↑ mortality, brain tissue pathology, early onset of virus in brain	Seth et al., 2003
VEEV	Cd, Mn	↑ mortality, brain tissue pathology, early onset of virus in brain	Seth et al., 2003

Microorganism	Chem./nutrient	Target effect of chem./ nutrient treatment	Reference
<i>Parasite</i>			
<i>L. major</i>	Fe suppl.	↓ parasite load, IL-4, IL-10, ↑ IFN, INOS, IgG	Bisti et al., 2000
<i>P. berghei</i>	PCB, HCB	↓ survival, ↑ uptake in lymphoreticular organs	Loose et al., 1978
<i>T. spiralis</i>	TBTO	↓ NK cell activity, G.I. expulsion of worms, ↑ muscle larvae	Vos et al., 1990
<i>T. spiralis</i>	TCDD	Delayed G.I clearance of parasites	Luebke et al., 1994
<i>T. spiralis</i>	TCDD	↓ resistance by both aging and TCDD	Luebke et al., 2000
<i>T. cruzi</i>	Se suppl.	↑ survival ↓ parasite load	Davis et al., 1998
<i>T. cruzi</i>	Se suppl.	↓ inflammatory lesions ↔ disease protection	de Souza et al., 2003
<i>T. cruzi</i>	Se deficiency.	↑ mortality, ↔ parasite load	de Souza et al., 2002
<i>T. cruzi</i>	Se deficiency.	↑ parasite load, severity of inflammatory lesions	Gomez et al., 2002
<i>T. lewisi</i>	Cd, Pb, Hg	↑ parasite load, IgG, IgM	Hogan and Lee, 1988
<i>T. musculi</i>	Se deficiency	↓ IgG, IgM	Ongele et al., 2002
<i>Fungi</i>			
<i>C. albicans</i>	Se deficiency	↑ microorganisms, ↓ neutrophils to kill microorg.	Boyne and Arthur, 1986

However, other infections have also been used as prototype infections in this area of research. Several recent host resistance studies on TCDD toxicity have employed various strains of influenza virus (House et al., 1990; Kerkvliet, 2002; Mitchell and Lawrence, 2003a; Nohara et al., 2002; Vorderstrasse et al., 2003), as well as bacterial (Dean et al., 1982; Luster et al., 1980; Vos et al., 1978) and parasitic infections (Dean et al., 1982; Luebke et al., 1994). The influenza viruses are RNA viruses of utmost concern among respiratory pathogens, notorious for yearly epidemics associated with excess morbidity and mortality. Furthermore, with intervals of decades pandemics occur with even higher mortality. The severity ranges from mild to severe respiratory tract infections, including pneumonia. The virus infects the epithelial cells in the respiratory tract resulting in an acute phase reaction with associated infection-induced changes in metabolism (Ilback et al., 1984a; Ilback et al., 1984b), as well as in a strong cell-mediated and humoral response (Burleson, 2000; Lebrec and Burleson, 1994; Vorderstrasse et al., 2003). After virus inhalation and internalisation in respiratory epithelial cells, antigen-presenting cells (APC) migrate to the regional lymph nodes where they present viral antigen and activate virus-specific T-lymphocytes. These events induce an immune cascade reaction of cytokines (IFN, IL-6, and TNF), which drive both B-cell activation and production of cytotoxic T-lymphocytes and neutralising antibodies (Kerkvliet, 2002; Lebrec and Burleson, 1994; Warren et al., 2000; Vorderstrasse et al., 2003).

Another commonly used experimental virus infection in rodents is murine cytomegalovirus (CMV) infection that is physically and biologi-

cally similar to human CMV. Human CMV is a ubiquitous herpesvirus that infects a large portion of the population and remains in the host in a latent state for a lifetime. It is usually subclinical, but clinical manifestations do occur. Consequently, infection of individuals with normal immune function may cause mild to moderate symptoms, including fever and malaise, and is accompanied by transient immunosuppression (Naniche and Oldstone, 2000). In immunosuppressed individuals, on the other hand, such as in transplant and AIDS patients, life-threatening disease is common. Immunosuppression, therefore, seems to be important for the development of disease and for the reactivation of latent virus. Antibodies play a role in neutralisation of viruses and in antibody dependent cell-mediated cytotoxicity (Van Loveren, 1995). NK-cells and IFN are both thought to be important in the early defence against CMV (Daniels et al., 1987), whereas macrophages have a doubtful role in resistance to CMV (Van Loveren, 1995).

A commonly used parasite infection model is *T. spiralis* infection in mice, a nematode parasite that resides in the small intestine (Dean et al., 1982; Luebke et al., 1994; Van Loveren, 1995; Vos et al., 1984). In this infection female parasites intestinally produce larvae that migrate via the bloodstream to striated muscle and sometimes to cardiac muscle and the central nervous system, where an inflammatory response ensues (Van Loveren, 1995). Once parasites have established themselves within the CNS, a progressive breakdown of neurological function accompanies the disease (Burchmore et al., 2002). A lack of T-cell mediated immunity results in failure to eliminate parasites from the intestine (Luebke et al., 1994). However, parasite-specific antibodies directed to the reproductive structure of female parasites, as well as for sensitisation of newborn larvae for attack by granulocytes and macrophages, seem to be important in the host resistance to infection. Infection with another parasite (*T. cruzi*) is associated with an acute and transient immunosuppression characterised by a decrease in both humoral and cellular responses, including down modulation of IL-2 that has been noted in both humans and mice (de Souza et al., 2002).

A few host resistance studies in rodents have also used strains of the protozoes *Plasmodium*, mainly *P. yoelii* and *P. berghei*. The host resistance appears multifaceted and involves specific antibodies, macrophages, and T-cell mediated arms of the immune defence (Van Loveren, 1995). Mortality and number of parasites in target organs have been used as endpoints of disease.

Among bacterial infections *S. pneumoniae* (Burleson, 2000; Strand et al., 2003), *S. aureus* (Bishayi and Sengupta, 2003; Boyne et al., 1986), and *L. monocytogenes* (Sugita-Konishi et al., 2003a; Vos et al., 1978) have been used as prototype infections in immunotoxicologic experiments in rodents to assess the effects of nutrients and chemical substances on host resistance. In the host defence to *S. pneumoniae* several immune

defence mechanisms participate. The complement system, primarily C3, seems to be a key mediator of host resistance to *S. pneumoniae* (Burleson, 2000), but also antigen-specific antibodies play a major role in controlling the infection (Van Loveren, 1995).

S. aureus is a virulent pathogen that, apart from serious systemic infections, has been known for a long time to produce acute food poisoning in man (Parrillo, 1993). The bacteria have the ability to produce enterotoxins (SE toxins); presently, 12 variants are known that are grouped into at least three families of SE toxins (Ilback et al., 2002). The major symptoms after exposure to SE toxins are vomiting and diarrhoea, but more severe intoxication may initiate a pathogenic cascade, resulting in hypotension and/or failure of multiple organ systems (Ilback et al., 2003c; Parrillo, 1993). Bacterial superantigens are the most potent known activators of human T-lymphocytes and induce T-cell cytotoxicity and cytokine production (Parrillo, 1993). However, a problem with this infection in experimental models is that rodents are practically insensitive to SE toxins (Ilback et al., 2003c).

Human *L. monocytogenes* infection is a significant health threat primarily to immunosuppressed individuals and is overwhelmingly a food-borne disease. After infection, *L. monocytogenes* is spread in the body and forms colonies in target organs such as the spleen, liver, and central nervous system (Roberts and Wiedmann, 2003). The defence against *L. monocytogenes* involves NK cells and phagocytosis by macrophages leading to clearance of microorganisms, as well as T cell-dependent lymphokine production that enhances phagocytosis (Dean et al., 1982; Roberts and Wiedmann, 2003; Van Loveren, 1995). After infection, 60-80% of the bacteria are killed in the liver, but those that survive continue to proliferate in the liver and spleen, giving rise to an infection that necessitates cell-mediated responses for defence (Roberts and Wiedmann, 2003). Consistent with the fact that *L. monocytogenes* is an intracellular pathogen, earlier data show that T cell-dependent immunity is important, whereas humoral immunity seems to be of less significance. Recent evidence, however, indicates that antibodies may play a previously unrecognised role (Roberts and Wiedmann, 2003). In target organs of infection histopathological lesions develop that are characterised by foci of inflammatory cells and debris.

3. Changed Metabolism in Infection

To attain a satisfactory functioning of the immune defence system a large amount of nutrients are required (Beisel, 1998), which is also likely true for active and replicating microorganisms in infected tissues. In the infected host the number of microorganisms can increase from just a few to literally millions during the course of a few days. Thus, the host' and the microorganisms' demands for nutrients run much in parallel. To meet the needs of the activated immune defence the host metabolic rate starts to increase during the incubation period of an infection and shows a sharp further increase as symptoms appear (Beisel, 1998). The acute phase of an infection is often associated with fever and it is generally estimated that, for every centigrade of increase, the metabolic rate increases by about 13% (Beisel, 1998).

Figur 2 Characteristic metabolic responses in a generalised infection involve changes in protein, carbohydrate, lipid, and trace element metabolism (Friman and Ilback, 1998).

Shift in metabolic pattern occurring as a host response to acute infection.

Despite that the need for certain nutrients dramatically increases, the infected individual loses appetite, which most often leads to a decreased intake of food. The body's own resources must therefore be mobilised, resulting in a changed metabolism of fat, protein and carbohydrates (Fig.

2). These metabolic alterations are part of the complex “acute phase reaction” (see “The acute phase reaction”).

The increased energy needed during infection is provided initially by a decrease in the normal protein synthesis rate, including down-regulation of the P450 system, and subsequently also through a simultaneous increased degradation of somatic tissues, including muscle protein from both red and white skeletal muscle (Beisel, 1998; Friman et al., 1984; Ilback et al., 1984a; Ilback et al., 1984c; Morgan, 1997). Even heart muscle protein is degraded (Friman et al., 1982; Ilback et al., 1983). The estimated amount of protein required to produce and maintain an increase in circulating leukocytes and acute phase proteins participating in host defence during major infections in man is 45 g/day (Grimble, 1996). Rats infected with *S. pneumoniae* or *S. typhimurium* showed a marked increase (up to 5 times) in the uptake of amino acids by the liver, whereas amino acids were lost from muscle tissue (Powanda and Beisel, 2003). Thus, regardless of the reduced intake of nutrients in infection, acute phase proteins are produced in excess by the liver, a condition shown to occur in infection even in protein-deficient children who exhibit kwashi-orkor, i.e. severe protein deficiency (Beisel, 1998).

Wasting of muscle tissue in infection is the result of a complex course of events in which classical hormones act in concert with proinflammatory cytokines, such as interleukins (IL-1, IL-6) and TNF, with the purpose of inhibiting protein synthesis and activating proteolysis in muscle (Fig. 2). In addition to acute phase protein synthesis, free amino acids released from this degradation of muscle protein can be recycled for de novo synthesis of, for example, antibodies and cytokines, as well as used in gluconeogenesis for energy production (Beisel, 1998; Beisel and Wannemacher, 1980).

The increased energy demand in infection is initially covered by carbohydrate fuels, resulting in an early hyperglycemia and hyperinsulinemia, followed by a progressive decrease of glucose from blood and glycogen from tissue stores (Beisel, 1991). Because stored carbohydrates only can fuel the host for a short period, endocrine responses to infection (insulin, glucagons, and growth hormone) activate the liver to use body resources of triglycerides, lactic acid, and gluconeogenic amino acids for glucose production (Beisel and Wannemacher, 1980). The accelerated use of carbohydrates is important for host defence mechanisms, such as the respiratory burst associated with phagocytic activity of neutrophils and macrophages (Beisel, 1998). If the production of glucose is disturbed, for example, because of a toxic insult of liver cells by xenobiotics, this may have severe consequences on the host defence, associated complications and survival.

The infection-induced metabolic responses in lipid metabolism are complex and less well-defined than those involving proteins and carbohydrates. TNF stimulates the release of free fatty acids from adipose tis-

sue cells and thereby contributes to the weight loss observed in chronic or repeated infections (Beisel, 1998). However, in most infections the increased blood insulin concentration counteracts the release of fatty acids from fat depots, which deprive the liver of substrate for the synthesis of energy-rich ketone bodies. Ketone bodies are an important metabolic fuel for the brain and other tissues during fasting and malnutrition in the absence of infection. In some infections triglycerides increase in blood, probably due to increased liver production in combination with a decrease in peripheral utilisation. In such infections fatty acids accumulate in hepatocytes in the form of lipid droplets that eventually may result in fatty metamorphosis or lipid degeneration (Beisel, 1998). A similar lipid accumulation also occurs in inflammatory lesions (Raymond et al., 1985) in target organs of infection, such as in the heart during CBV (Ilback et al., 1990) and *S. typhimurium* infections (Ilback et al., 1983).

An infectious disease is often accompanied by changes in several trace elements. Several trace elements are essential micronutrients required for various body functions and the well-being of the immune system, but also in preventing viral mutations which could change pathogenicity (Chaturvedi et al., 2004). The most consistent responses include a decrease in plasma levels of Fe and Zn and an increase in Cu (Beisel, 1998; Ilback et al., 2003b; Pekarek and Engelhardt, 1981). However, plasma changes in Mn, Mg, Co, Cr, I, and Gal have been described (Funseth et al., 2000a; Pekarek and Engelhardt, 1981). Because of analytical difficulties in measuring the low levels of trace elements in tissues, only a few studies of a limited number of infections describe trace element levels in infected organs (Funseth et al., 2000a; Ilback et al., 2000; Ilback et al., 2003a,b; Ilbäck et al., 2004). These specific trace element changes are discussed more deeply in the section "The acute phase reaction in infection".

4. The Acute Phase Reaction in Infection

In all infections an extensive adjustment in host metabolism occurs with the aim of mobilising all resources and activate all “functions” so that they are entirely directed towards protection to defeat the disease. Thus, the objectives of the responses are to disadvantage and destroy the invading microorganisms, repair damaged tissue, and restore tissue function to the normal condition. The course of a generalised infection can be divided into three parts, i.e. the incubation period, the acute disease, and the recovery period (Fig. 3). The host defence mobilisation is normally referred to as the “acute phase reaction” and is initiated during the early incubation period and peaks during fever. Host responses are similar in animals and man in a majority of acute infections (Beisel, 1998) and includes an array of responses, including fever, hormonal changes, immune cell activation, increased synthesis and release of cytokines, antibodies, complement and acute phase proteins, and a simultaneous flow of trace elements between blood and tissues, as well as extensive changes in various metabolic pathways (Beisel, 1998; Friman and Ilback, 1998; Friman et al., 1982; Funseth et al., 2000a; Grimble, 1996; Ilback et al., 1984a; Ilback et al., 2003b).

Figur 3 The acute phase reaction, modified from (Beisel, 1998). A generalised infectious disease can be divided in three parts, i.e., the incubation period, acute illness, and the convalescent period

The acute phase reaction of the host is mediated by cytokines, such as IL-1, IL-6 and TNF α , which, during infection and inflammation, are secreted by activated immune cells, including macrophages (Beisel, 1998; Grimble, 1996; Powanda and Beisel, 2003). The T-helper 1 (Th1) cytokines, represented by IFN γ and IL-2, favour cytotoxic T-cell responses, whereas the T-helper 2 (Th2) cytokines IL-4, IL-5 and IL-10 are thought to dampen cellular immunity and favour antibody responses (Naniche and Oldstone, 2000). IL-1 stimulates the secretion of IL-6 and glucocorticoids, both activating hepatic synthesis of MT and acute phase proteins (Brown, 1998; Coyle et al., 2002; Grimble, 1996). A five-fold increase in plasma proteins, consistent with the increase in acute phase proteins, has been detected in the early phase of lethal *S. pneumoniae* and *S. typhimurium* infections in the rat (Powanda and Beisel, 2003). Macrophages, monocytes, and lymphocytes are able to bind, catabolise and synthesize a variety of acute phase proteins, which may be a part of the host's immune modulation (Powanda and Beisel, 2003). These cytokine-mediated alterations in the host response appear to occur in proportion to the infectious dose and to the likelihood of death (Powanda and Beisel, 2003).

Acute phase proteins are metal-binding proteins, such as Fe-binding ferritin (Beisel, 1998), Cu-binding ceruloplasmin (Friman et al., 1982; Ilback et al., 1983), and the Cd- and Zn-binding MT (Funseth et al., 2002a; Ilback et al., 2004a). A temporarily changed trace element balance is therefore a part of the acute phase reaction and the changes in metabolism that generally appears in infections, as well as in inflammation that is due to other causes than infection (Beisel, 1998; Shenkin, 1995). Cytokines have been shown to upregulate the gene expression for the metal binding protein MT family (Borghesi et al., 1996; Palmiter, 1998). MTs are directly involved in Cd detoxification, Zn homeostasis, and protection of the cell from oxidative stress (Solis et al., 2002). Aside from the liver and kidneys, which are the main sources of MT, MTs are expressed to a certain extent in almost all mammalian tissues (Nordberg and Nordberg, 2000). For example, they are produced by thymic epithelial cells, suggesting an important role of MTs also in the growth and differentiation of the immune system (Borghesi et al., 1996). In the early phase of CB infection there is a five-fold increase in MT in the liver and kidneys (Ilback et al., 2004a). Thus, an infection-induced increase of MT in target organs of infection, such as the brain, pancreas, lymphocytes, liver, and kidneys, implies that potentially harmful metals could be taken up, if these are accessible in the blood, instead of the essential trace elements that normally are part of the protection against those injuries that are caused by the infection in the specific target organ.

Trace elements are required for the activity of a number of acute phase proteins and immune cells that directly participate and interact in host defence processes (Beisel, 1998; Shankar and Prasad, 1998; Shenkin, 1995). Already in the 1970s it was shown that volunteers exposed to live

attenuated Venezuelan equine encephalitis virus vaccine, as well as monkeys infected with *S. typhimurium*, responded with an early fall in serum Fe and Zn concomitant to a rise in Cu (Pekarek et al., 1970; Pekarek et al., 1975). An increased Cu/Zn quotient in blood has been used to indicate infection already before the development of clinical illness (Beisel, 1998; Ilback et al., 1983; Ilback et al., 2003b), and in vitro results of *S. enteritidis* infected enterocytes indicate that infection decreases absorption of Fe (Foster et al., 2001). Even at normal dietary trace element levels, the early infection induced MT elevation is associated with redistribution of essential as well as non-essential trace elements (e.g., a redistribution of Cd and Cu from the liver to the kidneys) (Ilback et al., 2004a). Toxic and essential metal interactions are well known to occur in the healthy individual (Goyer, 1997). Thus, during infection there is a flux in the body of both essential and non-essential trace elements that may cause an unfavourable balance and hence explain some of the changes in the toxicity of non-essential trace metals observed in target organs of common infections.

A negative consequence of the acute phase reaction, seen from a toxicological perspective, is that the synthesis of protein involved in less acute life important functions, including the liver enzymes in our detoxifying system (P450) for xenobiotics, such as TCDD and PBDE, has low priority and is down-regulated in virus (Darnerud et al., 2005; Funseth et al., 2002a), bacterial (Morgan, 1997), and parasitic infections (Luebke et al., 1994). Cytokines (IL-1, IL-6, TNF) produced during inflammation and infection have been shown to be of central importance for regulation of the P450 system (Morgan, 1997; Singh and Renton, 1981). The cytokine response varies in different infections, for example, *T. spiralis* stimulate the production of IL-1, IL-2, IL-5, and IFN γ (Luebke et al., 1994); *L. monocytogenes* stimulate IL-1 and IL-6 (Dyatlov and Lawrence, 2002); influenza simulate IL-2 and IFN γ (Warren et al., 2000); and CBV stimulate TNF and IFN γ (Ilback et al., 1993b). Cytochromes P450 are the products of a large gene superfamily where the specific forms of P450 enzymes can be selectively modulated by different cytokines (Morgan, 1997). Accordingly, different infections have the potential to affect differentially the P450 mediated detoxification of various xenobiotics in the host.

As shown for some infections, including CBV infection, the generalised acute phase reaction can be modified by nutrients and chemical substances in various ways; for instance, they could influence the severity of the infectious process, its duration, or its possible progression to subacute or chronic disease. The result of an infection is determined by a highly complex interaction between the microorganism and the host in which pharmacologically active substances (e.g., drugs), xenobiotics including non-essential trace elements (e.g., TCDD, Cd, and Hg) and nutrients (e.g., lipids, Se, Zn, and Fe) in our food and in the environment work interactively to produce a changed end-point.

5. Nutrients and Host Resistance

Almost all nutrients in the diet have been claimed to be crucial for an “optimal” immune response, but the requirement of specific nutrients for the various arms of the immune system has not been studied extensively. Both deficiency and excessive amounts of nutrients can adversely influence host resistance to a variety of pathogens (Chaturvedi et al., 2004; Field et al., 2002). Animal studies have illustrated that manipulations of a wide range of nutrients (amino acids, fatty acids, vitamins, and trace elements) can modulate many deleterious effects of infective and inflammatory states (Gimble, 1996). Malnutrition is a major cause of an insufficient immune system, which is worldwide being often recognised in poor populations where infections are a major health concern. The feeding of poor-quality silage seems to predispose farm animals to listeriosis (Roberts and Wiedmann, 2003). Malnourished CBV-infected mice showed increased virus persistence in target organs of infection and increased mortality, but this decrease in host resistance was completely reversed after a change to a normal diet (Woodruff, 1970; Woodruff and Kilbourne, 1970). In line with this observation influenza vaccinated subjects consuming an experimental nutritional formula containing antioxidants, Zn, Se, oligosaccharides, and triglycerides experienced enhanced immune function and fewer days of symptoms of upper respiratory tract infection (Langkamp-Henken et al., 2004). Daily multivitamin supplements have been found to reduce HIV disease progression in humans and to prolong the time before antiretroviral therapy is recommended (Fawzi et al., 2005)

It is not surprising that proteins are regarded as the most important nutrients in that immune cells have a high requirement of amino acids for cell division, antibody, and cytokine production (Beisel, 1998; Field et al., 2002). In addition, amino acids are used in the synthesis of acute phase proteins such as ferritin, ceruloplasmin, and MT (see the section “The acute phase reaction in infection”) (Beisel, 1998; Gimble, 1996), as well as for energy production by gluconeogenesis (see the section “Metabolism of nutrients and chemical substances in infection”) (Beisel, 1998; Beisel and Wannemacher, 1980)).

Although protein-energy malnutrition is cited as the major global cause of immunodeficiency, vitamins, fatty acids, and essential trace elements (Fe, Zn, Cu, and Se) are also important for immune function and host defence (Beisel, 1998; Field et al., 2002). Fatty acids serve as precursors for eicosanoids (prostaglandins, prostacyclins, thromboxanes, and lipoxines) that trigger many immune cell responses during infection and inflammation (Beisel, 1998). Lipids accumulate in inflammatory

lesions in the heart of CBV-infected mice, but the number of macrophages and cytotoxic and helper T-cells are not changed by a cholesterol-enriched diet (Ilback et al., 1990). However, hypercholesterolemia seems to decrease host resistance against CBV type B5 (CB5) in the mouse, but not based on increased replication of viruses (Loria et al., 1976). It was concluded that the increased mortality was due to a cumulative effect resulting from metabolic changes induced by the diet and from the infection. Experimental *M. avis* infection becomes more severe when mice receive a fat diet with high Fe content (Boelaert et al., 1996). This effect in *M. avis* infection may not be due to an adverse effect of fat on host resistance, but to an Fe-induced increase in microorganism growth because Fe is an essential nutrient for many pathogens (Foster et al., 2001; Lounis et al., 2001; Weinberg, 1999; Weiss, 2002) (see section "Altered virulence of microorganisms caused by nutrients and xenobiotics"). The ability of the host to sequester Fe is thus a primary defence mechanism against several bacterial infections. This contrasts to the finding that Fe loading of macrophages in vitro results in enhanced capacity to kill or to prevent replication of the intracellular microorganisms *L. monocytogenes* and *B. abortus* (Bisti et al., 2000). Thus, Fe seems to be a double-edged sword in infection and host resistance.

The normal trace element balance of, for example, Cu and Zn is changed in target organs of infections and other inflammatory processes (Beisel, 1998; Funseth et al., 2000b; Ilback et al., 2003b). This flux of trace elements is mediated by metal transporting proteins, such as MT (Zn, Cu), ceruloplasmin (Cu) and ferritin (Fe). Trace elements are also important for the activity of certain enzymes involved in these processes, including superoxide dismutase (Cu, Zn, Se) and glutathione peroxidase (Se). Zn plays a central role in enzyme-catalysed reactions of protein synthesis, and both Cu and Fe are part of the cytochrome system and Se is required for glutathione peroxidase activity and free radical scavenging (Shenkin, 1995).

Numerous studies have shown that Zn deficient animals are more susceptible to a diverse range of infectious agents, including viruses (HSV, SFV), bacteria (*L. monocytogenes*, *S. enteridis*, *M. tuberculosis*), protozoan parasites (*T. cruzi*), eukaryotes (*C. albicans*), and helminths (*T. spiralis*) (Shankar and Prasad, 1998). Zinc is important for the functioning of the immune cells (Driessen et al., 1995) and Zn-deficient persons experience an increased susceptibility to a variety of pathogens (Shankar and Prasad, 1998). Zn supplementation has been found to reduce the disease burden in pneumonia and other respiratory infections in children (Bhandari et al., 2002; Bhaskaram, 2002), as well as to beneficially affect the course of the common cold (Prasad et al., 2000).

Humans suffering from Chagas' disease (caused by *T. cruzi*) have low levels of Se in the heart where *T. cruzi* is harboured (de Souza et al., 2003; Rivera et al., 2002). Accordingly, in experimental *T. cruzi* infection

Se deficiency increases parasitemia and the severity of inflammation (Gomez et al., 2002), whereas supplementation limits the replication of *T. cruzi* parasites resulting in decreased parasitemia and increased longevity (Davis et al., 1998). New data suggest that Se supplementation does not lead to a general protection during *T. cruzi* infection, but may help protect the heart from inflammatory lesions, which are secondary to the existence of *T. cruzi* (de Souza et al., 2003). There is also a strong link between Se deficiency and viral infection as causative agents in the cardiomyopathy of Keshan disease (Beck and Levander, 2000). The oxidative stress of the host can have a profound influence on a viral pathogen (Beck and Levander, 2000) and the antioxidant properties of Se are important when macrophages and neutrophils release increased quantities of superoxides and hydrogen peroxides during digestion of invading microorganisms (Davis et al., 1998). Mice deficient in Se or vitamin E, a nutritional antioxidant like Se, are more susceptible to the development of virus-induced inflammatory lesions in both influenza (Beck et al., 2001) and CBV infection (Beck et al., 1994). In experimental *C. albicans* infection in steers neutrophils from Se deficient cattle were less able to kill *C. albicans* than were neutrophils from cattle with normal Se levels (Boyne and Arthur, 1979); analogous results were found for *S. aureus* infected cows (Gyang et al., 1984). Further, Se-deficient rodents showed impaired ability of neutrophils to kill *C. albicans* and *S. aureus* (Boyne and Arthur, 1986; Boyne et al., 1986), resulting in more microorganisms in target organs of infection.

Trace elements are known to affect cell death in normal cells (Shen et al., 2001), but it is practically unknown how they affect cell death in the infected host. A number of studies have demonstrated that a lack of Zn caused by chelation can trigger cell death in virus-transformed cells (Fernandez-Pol et al., 2001), but data have also been published showing that, for example, dengue virus type 2-induced cell death increases at high extracellular Zn concentrations (Shafee and AbuBakar, 2002). The macrophage, a pivotal cell in many immunologic functions, is known to be adversely affected by Zn deficiency, which can dysregulate intracellular killing, cytokine production, and phagocytosis (Shankar and Prasad, 1998).

6. Effects of Xenobiotics on Host Resistance

Important negative effects of potentially harmful xenobiotics present in the environment and in food have been shown to be directed against our immune system, which in the long term, could affect our susceptibility to infections and autoimmune diseases (Burchiel, 1999; Van Loveren et al., 1998; Zelikoff et al., 1994). A chemical substance could disturb the normal homeostasis of the immune system, resulting in enhanced pathogen invasion and growth and tissue damage, or in immune-mediated toxicity on the immune system itself, or on other organ systems. The immune system seems particularly sensitive to modulation by certain classes of environmental chemicals, including polycyclic aromatic hydrocarbons (PAHs), halogenated aromatic hydrocarbons (such as TCDD), and non-essential trace elements (such as Pb, Cd, Hg and Ni) that are all common pollutants in the food and the environment. A number of potentially toxic metals have even been ranked in terms of their immunosuppressive qualities, i.e., Hg>Cu>Mn>Co>Cd>Cr (Lawrence, 1981). However, it is important to distinguish between small and biologically unimportant changes in immune parameters presumed to be without health consequences and those changes that may jeopardise our host defence. In many studies an alteration in immune function has been observed in the absence of a demonstrable change in host resistance (Kimber and Dearman, 2002).

In an early paper from 1966 by Selye et al (Selye et al., 1966) it was shown that a normally well-tolerated dose of Pb increases the sensitivity to endotoxins of various gram-negative bacteria and that the adverse effect is greatest when the two compounds are given simultaneously. Endotoxin is the major determinant for severe disease following infections by gram-negative bacteria. Moreover, infection-induced mortality resulting from western encephalitis virus was reduced when As was administered before virus inoculation, whereas As administered during ongoing infection increased mortality (Gainer and Pry, 1972). Thus, different experimental conditions in terms of animal strain and species, type and strain of microorganism, as well as dose and route of administration and test substance regimen may greatly affect outcome of an infection.

In another early study (Thomas and Hinsdill, 1978) it was shown that monkeys fed with PCB levels (5 ppm) close to those accepted in certain foods had significantly lower γ -globulin levels, as well as lower antibody titres after immunisation with sheep red blood cells. Later studies using Ni, Hg, Pb, and Cd, as well as organohalogen compounds, such as PCB

and TCDD, have supported that xenobiotics have variable effects on those arms of the immune system known to be important for our host defence against infection (Descotes and Vial, 1994; Ellermann-Eriksen et al., 1994; Funseth and Ilback, 1992; Gomez et al., 2002; Ilback, 1991; Ilback et al., 1994a,b; Ilback et al., 1996; Imanishi et al., 1980; Lee et al., 2002; Seth et al., 2003). However, the *in vivo* impact and consequences of the various immunotoxic effects of chemical substances on host resistance to infection have only been studied in a limited number of infections, sometimes with conflicting results.

A complex and finely tuned relationship appears to exist between the immune system and the neuroendocrine system, where many detrimental outcomes on health have been posited to relate to neuroendocrine immune interactions (Friedman and Lawrence, 2002). Thus, some environmental pollutants, such as Hg and Pb, are classified as both neurotoxins and immunotoxicants. Estrogens are not only essential for reproduction but are also immunomodulating agents affecting host resistance and elimination of microorganisms (Kittas and Henry, 1980; Luster et al., 1984; Pung et al., 1984). Macrophages have even been reported to have classical cytosolic oestrogen receptors (Ma et al., 2003). Safety evaluation of chemicals with steroidal and non-steroidal structures, and thus with varying degrees of estrogenicity, has shown that their immunotoxicity, for the most part, correlates with estrogenicity (Luster et al., 1984). Furthermore, a number of metals (e.g., Cd and Pb) and organo-halogen compounds (e.g., PCB and DDT) have been shown to have hormone-disturbing effects (Kaiser, 2000; Safe, 2003), which, at immune activation and infection, can likely further strengthen the toxic effects of these chemical substances in the infected host. It was recently shown that parasitic (*Moniliformis moniliformis*) infection and Cd exposure affect stress hormone (cortisol) levels in an additive manner (Klar and Sures, 2004). Diethylstilbestrol (DES), a typical oestrogen-like chemical, has been shown in mice to induce immune suppression and reduce elimination of bacteria (*L. Monocytogenes*) (Pung et al., 1984) and parasites (*T. spiralis*) (Luebke et al., 1994), possibly because of reduced mobilisation of phagocytising macrophages (Pung et al., 1984). Similarly, the endocrine disrupter bisphenol A, a constituent of certain plastic packaging materials for food, reduced the elimination of *E. coli* in experimentally infected mice (Sugita-Konishi et al., 2003b).

Injury to the immune system caused by chemical substances or a shortage of important nutrients can therefore lead to an increased susceptibility to infections, but subsequently also to an altered course of the clinical disease, such as chronic inflammation and a delayed healing process in organs affected by the infection (Christensen et al., 1996; Funseth et al., 2002b; Ilback et al., 1994a; Ilback et al., 1996). Because of their ability to migrate and phagocytise, as well as to present antigens to T-helper cells, macrophages play an important role against viral, para-

sitic, and bacterial infections, as well as in the healing of associated tissue lesions (Bishayi and Sengupta, 2003; Ilback et al., 1989; Van Loveren, 1995; Vos et al., 1990). In the presence of Th1 cell cytokines (IFN γ , TNF), macrophages are activated and their capability for killing intracellular microorganisms (e.g., viruses) greatly enhanced (Ma et al., 2003). However, when Th2 cell cytokines (IL-4, IL-13) are present, macrophages become activated in an alternative way to combat parasitic and extracellular pathogens (e.g., the majority of bacteria). Macrophages are known to be mobilised to inflammatory tissue lesions and, in the infected inflamed heart of CBV-infected mice, the number of these cells is correlated to the size of the inflammatory lesions (Ilback et al., 1989; Ilback et al., 1990). A reduced bacterial clearance of *S. aureus* has been noted in both blood and spleen in As- and Pb-exposed rats and this was associated with a reduced chemotactic migration of macrophages (Bishayi and Sengupta, 2003). In fact, the immune responses to any pathogen requires a tightly controlled balance between the mechanisms bringing about the pathogen elimination and the mechanisms governing the repair of damaged tissue. Whereas controlled inflammation is beneficial, aberrant function of immune cells induced by xenobiotics may disturb this balance and result in enhanced tissue damage.

Non-essential and potentially toxic trace elements (Cd, Hg) can, if they are present in sufficient amounts, compete with essential elements (Cu, Se, Zn) in the body (Glynn et al., 1993; Goyer, 1997). MTs are induced in several organs by Cd, cytokines, and infection (see section "Acute phase reaction in infection"), but in addition to Cd, MTs have the capacity of binding Zn, Cu, Hg, and As (Lu et al., 2001; Nordberg and Nordberg, 2000; Toyama et al., 2002). MTs can interact with the plasma membrane of lymphocytes and alter immune cell function, including causing increased cell proliferation (Borghesi et al., 1996). Much of the toxicity, toxicokinetics, and biochemistry of essential and toxic metals are often related to MTs (Ilback et al., 2004a; Nordberg and Nordberg, 2000). A competition between non-essential and essential trace elements may limit availability of essential nutrients for healing of inflammatory lesions and clearance of microorganisms in target organs of infection (see section "Interactions between infection, nutrients and xenobiotics")

7. Altered Virulence of Microorganisms Caused by Nutrients and Xenobiotics

Chemical substances in food or lack of essential nutrients can, in connection with infection, potentially lead to changed conditions for the replicating microorganism in a direction that could be unfavourable for the infected host. From cell culture studies, microorganisms are known to be highly sensitive to the environment they grow in. Metal ions are important components in several gene regulatory proteins, including virus proteins (Fernandez-Pol et al., 2001). Essential virus and cellular Cu- and Zn-containing metal proteins are being studied intensively as key factors in the control and prevention of virus infection (Fernandez-Pol et al., 2001). Thus, in the infected host some information exists concerning how nutrients and chemicals influence the susceptibility to pathogens and the infection-replication phase, as well as how they affect the growth and virulence of microorganisms in infected tissues. However, from present data it is in most cases extremely difficult to evaluate whether an increased number of microorganisms is due to an immunotoxic effect or an actual effect on the specific microorganism. Moreover, all essential nutrients, as well as the majority of xenobiotics have not yet been studied from these aspects.

The Cu-containing ceruloplasmin is an important acute-phase reactant in generalised infections (Beisel, 1998) and the Cu level in plasma is known to increase in infections that are caused by various microorganisms (Beisel, 1998; Friman et al., 1982; Ilback et al., 2003b). Data on effects of Cu on virulence and growth of microorganisms in the host are limited, however. One study shows that the number of *T. lewisi* parasites in blood was twice as high in Cu-deficient rats compared with controls (Ongele et al., 2002). Another study has implicated a role of Cu in the pathogenesis of neuronal injury in Alzheimer's disease and the prion-induced encephalopathies (Waggoner et al., 1999).

To what extent the availability of Zn affects in vivo growth of infectious agents themselves is not clear, but it is known that most microorganisms require Zn for basic cellular processes (Shankar and Prasad, 1998). Chelation of Zn can reduce the growth of *C. albicans* (Sohnle et al., 2001), whereas lack of Zn has been shown to increase the risk of *S. pneumoniae* infection to take a serious course (Strand et al., 2001), as well as cause a four-fold increase of *T. musculi* parasites in the blood in experimental *T. musculi* infection (Ongele et al., 2002). Inhibition of

DNA replication in *S. enteritidis* after nitrogen oxide exposure is accompanied by Zn mobilisation, which implies that DNA-binding Zn metalloproteins are critical targets of antimicrobial activity (Schapiro et al., 2003). In accordance with observations in the above studies, electron microscopy studies on HSV have demonstrated massive deposition of Zn onto HSV virions, which interfered with glycoprotein-mediated fusion (Suara and Crowe, 2004).

Many pathogens (fungi, protozoa, bacteria) must acquire Fe from their host to survive and increase in number (Weinberg, 1999; Weiss, 2002). In *S. aureus* heme Fe seems to be the preferred Fe source during the initiation of infection (Skaar et al., 2004). Many gram-negative bacteria have evolved very efficient mechanisms for scavenging Fe from mammalian Fe-binding proteins. For example, *E. coli* and *K. aerogenes* produce extracellular Fe chelators, *L. monocytogenes* can remove and get access to Fe by chemically reducing Fe and its affinity for the chelator, whereas other bacteria have specific receptors for transferrin and lactoferrin and their chelated Fe. In persons whose tissues and cells contain excessive Fe, invading pathogens can much more readily procure Fe (Weinberg, 1999). Accordingly, several experimental and epidemiological studies show that excess of Fe can worsen the outcome of infectious diseases, such as human listeriosis (Roberts and Wiedmann, 2003), tuberculosis, HIV, and hepatitis C (Lounis et al., 2001; Weiss, 2002). In several intracellular infections (parasitic, bacterial, viral) the disease-aggravating potential of Fe seems to be related to loss of the macrophages' ability to kill the pathogen by cytokine-dependent (mainly IFN γ) effector pathways (Serafin-Lopez et al., 2004; Weinberg, 1999). Proinflammatory cytokines and IFN γ stimulate the production of nitric oxide, which is a highly microbicidal and parasitocidal agent (Beisel, 1998).

Somewhat unexpectedly, the susceptibility to parasite infection with *L. major* can be suppressed with Fe supplementation (Bisti et al., 2000). Results indicate, however, that *C. pneumoniae* is dependent on Fe for its growth (Al-Younes et al., 2001; Freidank et al., 2001), and that a greater availability of Fe increases the virulence of *S. enteritidis* bacteria (Foster et al., 2001) and stimulates the growth of *M. tuberculosis* (Serafin-Lopez et al., 2004). From data in *S. enteritis* infected Caco-2 cells it has been suggested that an elevated enterocyte Fe status increases the susceptibility to infection and exacerbates the mucosal inflammatory response because of increased cytokine expression (Foster et al., 2001). Similarly, an excess of Fe in human *M. tuberculosis* infection produces a more severe disease course (Lounis et al., 2001). The amount of Fe that is taken up in the sclerotic cardiac valves in patients with *C. pneumoniae* bacteria in their valves shows a clear association with the degree of calcified, damaged tissue (Nystrom-Rosander et al., 2003).

Essential trace elements evidently have the ability to affect the growth of microorganisms. A few studies have shown that also changes in non-

essential trace elements can affect both growth and virulence of microorganisms. *Helicobacter pylori* has well-developed metal ion homeostatic systems but these fail to regulate high levels of Co within the bacteria, allowing toxic levels to be reached (Bruggraber et al., 2004). Pb exposure increases virus multiplication and disease development in mice infected with SFV (Gupta et al., 2002). In EMCV infection Hg (Koller, 1975) and Co (Gainer, 1972) increased the mortality, and in Co-exposed mice the amount of virus and the concentration of Co in the spleen and heart increased. Although Cd disturbs the host's defence system against *L. monocytogenes* (Thomas et al., 1985), EMCV (Exon et al., 1979), CMV (Daniels et al., 1987), and influenza virus (Chaumard et al., 1991; Thomas et al., 1985), organism titres do not seem to be influenced. However, Cd seems to induce a dose-related increase in the susceptibility to HSV (Thomas et al., 1985). Both Cd and Mn cause an earlier virus attack and more extensive pathological changes in the brain in EMCV, SFV, and VEEV infection (Seth et al., 2003). Higher levels of *T. lewisi* parasites in blood and prolonged disease compared with controls have been reported in rats exposed to Cd, Pb, and Hg (Hogan and Lee, 1988). It can be concluded that different non-essential trace metals are of varying habitual importance for different microorganisms, as well as for the end-point of disease.

Arsenic was early shown to increase mortality in PRV, EMCV, and SLEV infection in mice (Gainer and Pry, 1972). A few years ago As was reported to enhance HIV-1 infectivity (Turelli et al. 2001) and recently it was shown that As stimulates retroviral reverse transcription, possibly via effects on mitochondria (Berthoux et al., 2003). Moreover, As accelerated the kinetics of spreading of HIV infection in the T cells and the number of cells containing HIV-1 provirus (Berthoux et al., 2003). However, As had no detectable effects on viral expression post-integration or virion assembly. On the other hand, As has been shown to be a potent inhibitor of Hepatitis C virus replication, possibly by interfering with cellular factors necessary for replication (Hwang et al., 2004). A similar result was obtained for HSV, where As increased the stability of the replication protein compartments that need to be disrupted for successful replication and production of progeny virus (Burkham et al., 2001).

Ca increases infectivity of rotaviruses and this does not seem to be due to changed surface properties in host cells, but rather to conformation changes of virus particles (Pando et al., 2002). Besides being important for the immune system, certain trace elements possess antioxidant functions that possibly can alter the genomes of microorganisms, particularly of viruses (Bhaskaram, 2002). Se deficiency produces genetic changes in replicating influenza virus and more serious lung injuries (Beck et al., 2001; Nelson et al., 2001). With respect to CBV, a lack of Se can result in increased virulence (Beck et al., 1994), whereas supplementation mitigates infection (Ilbäck et al., 1989; Ilback et al., 1998). Mn can change

the virulence of retroviruses, including HIV (Vartanian et al., 1999) and genes inserted into the human CMV genome can be expressed by metals such as Zn (Takekoshi et al., 1993). Cd has even been shown to reactivate HSV in latent infected mice (Fawl et al., 1996).

The mortality of ducks (Friend and Trainer, 1970) and mice (Imanishi et al., 1980), infected with HSV was increased after PCB exposure, but no difference in inducibility of interferon was noted in the mice. Even with no signs of PCB intoxication, PCB-exposed mice challenged with *S. typhimurium* showed higher mortality and increased number of viable organisms in the spleen, liver, and blood than did non-exposed mice (Thomas and Hinsdill, 1978). Moreover, significantly more larvae from parasites (*T. spiralis*) in the small intestine have been shown to be released and recovered in muscle of TCDD exposed mice than in non-exposed mice (Luebke et al., 1994). Because of the more complex genomic structure of parasites than viruses, it seems unlikely that a specific genetic mutation is responsible for the increased parasite growth and virulence following TCDD exposure (Rivera et al., 2003). Instead, exogenic factors will have to be considered. Synergistic effects of nutrients and chemical substances in food and the environment can thus be important factors in “emerging and re-emerging infections” (Bhaskaram, 2002; Gauntt and Tracy, 1995; Morse, 1997).

8. Gastrointestinal Absorption of Nutrients and Chemical Substances in Infection

As noted earlier, infections in general change the metabolism and the uptake of nutrients from the gastrointestinal tract. The absorption of individual amino acids from the intestine may be depressed and delayed or increased depending on the infection studied (Beisel, 1998). Food components in the gastrointestinal tract can also markedly alter the bioavailability of chemical substances (Ilbäck et al., 2004b). For example, pre-clinical studies have shown that the bioavailability of the broad spectrum antipicornaviral drug Pleconaril is markedly enhanced together with food, with roughly a seven-fold difference in bioavailability between fed and fasting states (Abdel-Rahman and Kearns, 1998).

It has been proposed that in healthy individuals lipids cause damage to the gastrointestinal epithelium, which may also increase the uptake of toxic substances into the circulation (Ilbäck et al., 2004). Thus, it is reasonable to assume that an increased gastrointestinal lipid absorption in infection is accompanied by an increased absorption of lipid soluble xenobiotics. However, whether and to what extent infections can alter the gastrointestinal uptake of various chemical substances has only been studied in a limited number of experimental infections.

Enterocytes are able to synthesise and secrete a variety of immunomodulatory molecules (e.g., cytokines, chemokines, and growth factors) (Foster et al., 2001). The colonic epithelial barrier function seems to be reduced by cytokines (e.g., IFN γ , IL-4, and IL-10) and there are convincing data that the proinflammatory cytokines TNF α and IFN γ can act synergistically to reduce epithelial cell barrier function (Walsh et al., 2000). Host dependent zonulin secretion, a modulator of small intestinal tight junctions, caused an impairment of the barrier function after exposure of rabbit jejunum to infection with *S. typhimurium* and *E. coli* (El Asmar et al., 2002). *Vibrio cholerae* toxin and other bacterial toxins have been found to increase the permeability of the small intestinal mucosa by affecting the structure of the intercellular tight junctions (Fasano et al., 1991). Zn seems to protect the intestinal cells from *E. coli* by inhibiting the adhesion and internalisation of bacteria, preventing the increase of tight junction permeability and modulating cytokine gene expression (Roselli et al., 2003). Both Se and vitamin E seem to be required for specific IL-4 related changes in intestinal physiology that promote host

protection in mice against the gastrointestinal parasite *Heligmosomoides polygyrus* (Smith et al., 1998)

The early fall in plasma Fe in infection (Beisel, 1998) may be explained by in vitro results showing a decreased intestinal absorption of Fe and a concomitantly increased Fe concentration of *S. enteritis* infected enterocytes (Foster et al., 2001). Accordingly, clinical studies in patients carrying *Helicobacter pylori* evidenced impaired Fe absorption (Ciacci et al., 2004). Part of the sequential changes that occur in blood trace element levels of infected individuals probably reflect toxic and essential element interactions and a changed gastrointestinal absorption. In line with this view, supplementation of the diet with the essential trace element Se results in increased gastrointestinal uptake and improved Se status, which leads to enhanced survival capability and diminished virus-induced inflammatory heart damage in CB3 infection (Ilback et al., 1998).

Interactions between essential and non-essential trace elements are well known (Goyer, 1997). When Se is present in the gastrointestinal tract, it can reduce the uptake of Hg (Glynn et al., 1993). In vitro studies show that Zn deficiency alters the barrier function of porcine endothelial cells, whereas Zn supplementation prevents TNF-induced disruption of the cell membrane of the cell monolayer (Roselli et al., 2003). Cd competes with Zn (Goyer, 1997) and Zn supplementation seems to reduce gastrointestinal absorption and accumulation of Cd, whereas Zn deficiency intensifies Cd accumulation and toxicity (Brzoska and Moniuszko-Jakoniuk, 2001). After oral administration of Cd, the CBV infection induces an increased and dose-dependent uptake of Cd from the gastrointestinal tract (Fig. 3)(Glynn et al., 1998). An increased exposure

Figure 4 Dose-dependent Cd accumulation in selected organs in control and and CBV-infected mice 24 hours after a single oral Cd dose (Glynn et al., 1998)

of Hg and Ni via food intake during CBV infection in mice increases tissue accumulation of these metals, as well as the size of the virus-induced inflammatory lesions in the heart (Ilback et al., 1992a; Ilback et al., 1994a; Ilback et al., 1996). Hg administered in food has also been shown to change the trace element balance in the infected and inflamed heart, indicating changed gastrointestinal uptake during infection (Ilback et al., 2000). Consistent with this observation, it has been found that harbour porpoises dying of infectious diseases caused by parasite, bacterial, fungal, and viral pathogens had increased contents of Zn, Hg, and Se, as well as an increase in the Hg/Se molar ratio in the liver (Bennett et al., 2001), indicating a disturbed absorption and trace element balance.

9. Tissue Distribution of Nutrients and Xenobiotics in Infection

Animal models using both virus (CBV) and bacterial (*S. typhimurium*) infections have shown accumulation of several lipid fractions in inflammatory lesions in target organs of infection (Ilback et al., 1984c; Ilback et al., 1990). A concomitant accumulation of the lipid soluble TCDD in the thymus, spleen, pancreas, brain, and liver is associated with these lesions in CBV infection (Funseth and Ilback, 1994). This organ distribution pattern contrasts to the distribution of another lipid soluble compound, i.e. PBDE, which, in CBV infection, mainly accumulates in the liver but not in the pancreas, thymus, spleen, or brain (Darnerud et al., 2005). In fact, PBDE exhibits decreased uptake in the pancreas.

As a response to CBV infection in normally fed mice the normal balance of both essential and non-essential trace elements is changed in target organs of infection (Funseth et al., 2000b; Ilback et al., 2003b). For example, Cu and Cd accumulate in the liver and kidneys to various extents (Ilback et al., 2004a); Ca, Zn, Se, and Cu accumulate in the heart (Funseth et al., 2000b; Ilback et al., 2003b); and Ca, Cu, V, and Mg accumulate in the pancreas (Ilback et al., 2003a). In the brain there is a concomitant accumulation of Se and Hg (Ilbäck et al., 2005a), as well as an increased content of Cu (Ilbäck et al., 2004b). An increased Fe accumulation is also known to occur in the liver in human hepatitis C virus infection (Weiss, 2002), in the brain of HIV-infected humans (Boelaert et al., 1996), in the brain of scrapie-infected mice (Kim et al., 2000), and in human sclerotic cardiac valves that harbour *C. pneumoniae* (Nystrom-Rosander et al., 2003).

During CBV infection, potentially toxic chemical substances to which the individual has been exposed, including Ni, Cd, Hg, TCDD, PBDE, and acrylamide, will be distributed quantitatively differently in the body as compared with a healthy individual (Figs. 5 and 6). For instance, Ni is accumulated in the pancreas and heart (Ilback et al., 1992a; Ilback et al., 1994a), Cd in the spleen and kidneys (Ilback et al., 1992b), TCDD in the brain and thymus (Funseth and Ilback, 1994), acrylamide in the blood and thymus (Abramsson-Zetterberg et al., 2005), and PBDE in the liver (Darnerud et al., 2005). When Hg and Ni (Ilback et al., 1994a; Ilback et al., 1996), but not Cd (Ilback et al., 1994b), is administered in food during CBV infection, inflammatory lesions and damage to the heart are increased. Moreover, Hg-exposed mice show viruses that are more persis-

tent (Ilback et al., 1996) and a changed balance of Zn and Ca in the inflammatory lesions in the heart (Ilback et al., 2000). Cd exposure during ongoing infection, on the other hand, affects the normal trace element homeostasis resulting, in increased Cu and Fe concentrations in the brain and where Fe accumulates in focal deposits (Ilbäck et al., 2005b). Thus, an infection-induced down-regulation of the detoxifying capacity (P450 system) and induction of metal-binding proteins, including competition between essential and non-essential trace elements, can account for an unfavourable trace element balance in infected organs, as well as an increased retention of potentially toxic xenobiotics (see previous sections on absorption and metabolism), disturbed clearance of microorganisms, and adverse effects on the healing of inflammatory lesions.

Figure 5 . Whole-body autoradiogram of Cd distribution in a non-infected mouse (A) and a CBV infected (B) mouse (Ilback et al., 1992b).

Fig. A

Fig. B

Figur 6 Whole-body autoradiogram of Ni distribution 10 min after administration in a non-infected mouse (A), at 10 min after administration in a CBV-infected mouse (B), and at 4 hours after administration in a CBV-infected mouse (C) (Ilback et al., 1992a)

Fig. B

Fig. C

10. Metabolism of Nutrients and Xenobiotics in Infection

As described previously, the acute phase reaction during infection results in a down-regulation of the detoxifying system (Darnerud et al., 2005; Morgan, 1997) but in an increased synthesis of metal-binding proteins important for host defence. Two such proteins are ceruloplasmin (a Cu-containing protein) (Friman et al., 1982; Ilback et al., 1983) and MT (Funseth et al., 2002a; Ilbäck et al. 2004a). During early CBV infection, (Ilback et al., 1983) the amount of MT increases about five-fold in the liver and kidneys (Funseth et al., 2002a; Ilback et al., 2004a). This induction of MT, even at normal physiological levels of trace elements, results in redistribution of Cd and Cu from the liver to the kidneys (Ilback et al., 2004a). Influenza infection has also been shown to induce gene expression of MT in both the liver and the lungs (Ghoshal et al., 2001). With increased capacity of binding, MT can bind Zn, Cd, Hg, and Cu (Nordberg and Nordberg, 2000), but interactions with other metals cannot be excluded when these are present in large quantities or when there is a shortage of essential trace elements (Goyer, 1997). The infection-associated induction of metal-binding proteins can account for an altered trace element balance in infected organs and a prolonged persistent accumulation of chemicals in target organs of infection that may affect the growth and virulence of microorganisms, as well as repair processes in inflammatory tissue lesions.

Because of the increased energy need during infection, the synthesis of proteins not necessary for the host defence is down-regulated (Beisel, 1998). In accordance with this observation is the observed down-regulation of the detoxifying P450 system that is not essential for the combat of the infection (Funseth et al., 2002a; Darnerud et al., 2005). The P450 system is required for the detoxification of several hazardous compounds, including TCDD, PCB, PBDE, and acrylamide (Morgan, 1997). TCDD is one of our most problematic environmental contaminants. It is fat soluble, accumulates successively during the lifetime of the exposed individual, providing the exposure exceeds the detoxifying capacity of the P450 system, stored in depots, including fatty tissues (Funseth and Ilback, 1994). The P450 system (Cyp 1A1/Cyp1A2) metabolises TCDD and PBDE, where it seems that infection affects both enzyme families as well as the tissue distribution of TCDD (Funseth and Ilback, 1994) and PBDE (Darnerud et al., 2005), although with a different distribution pattern of these compounds.

In addition to the degradation of proteins, primarily from muscle tissue (Friman et al., 1984), there is also in more long-lasting infections degradation of stored body fat (Beisel, 1998). This degradation of fat depots may result in release of previously accumulated xenobiotics (e.g., TCDD) from fat tissue into the blood (Funseth et al., 2000c). This released TCDD can be freely redistributed to various organs, including vital organs that are often targets of the infection (Fig. 7) (Funseth et al., 2000c). This probably occurs because the detoxifying P450 system is down-regulated by the infection (Funseth et al., 2002a) and because inflammatory lesions cause concomitant lipid accumulation in the target organs of infection (Ilback et al., 1984c; Ilback et al., 1990; Raymond et al., 1985). Consistent with this finding, a potential association between chronic exposure to PCBs and infectious disease mortality has been found in harbour porpoises (Jepson et al., 1999). This means that during the short period of an infection a long-term or life-time storage of dioxin can be released in large quantities and redistributed to such vital organs as the thymus and brain (Funseth et al., 2000c).

Figur 7 Redistribution of TCDD over time in non-infected control mice (o) and CBV-infected mice (●) in blood, brain, and thymus at days 0, 4, and 7 after inoculation of virus (Funseth et al., 2000c).

11. Excretion of Nutrients and Xenobiotics in Infection

The increased uptake of, for example Cd, Ni, and TCDD, in target organs of infection seems to be associated with a more long-term accumulation of these chemical substances in the target organs (Funseth et al., 2000c; Ilback et al., 1992a; Ilback et al., 1992b). One explanation for this association might be that certain potential toxic trace elements compete as well as bind more efficiently and strongly to infection-induced proteins (such as MT) when there is an excess in relation to the physiological concentrations of essential trace elements. In CBV infection a pronounced decrease in As occurs in the target organs of this infection before the inflammatory processes are initiated (Benyamin et al., 2005), whereas Cd in this early phase of disease accumulates in the same organs (Ilback et al., 1992b). Because MT is known to bind both As (Toyama et al., 2002) and Cd (Nordberg and Nordberg, 2000), these results may indicate that Cd competes and has a higher affinity for MT than As. Thus, there seems to exist a competition not only between essential and non-essential trace elements (Goyer, 1997), but also between different non-essential trace elements in infected tissues.

This explanation is consistent with the fact that the induction of MT that occurs during infection causes a dose-dependent increase in the gastrointestinal and in the target organ uptake of Cd (e.g., liver and kidney) (Glynn et al., 1998). Because Cd is strongly bound to MT and therefore accumulated (Ilback et al., 1992b; Nordberg and Nordberg, 2000), an infection-induced increase in uptake and a concomitant reduced excretion can, with several infectious episodes over time, be expected to result in injuries and disturbed organ (e.g., liver and kidney) function. When it comes to Ni, it seems to remain for long periods in infected-inflamed tissues (e.g., pancreas and heart, Fig. 6), which is probably due to an accumulation in macrophages that are mobilised to the injured area to participate in the healing process (Ilback et al., 1994a; Ilback et al., 1990).

In several infections accumulation of fat occurs in infected tissues, often accompanied by tissue necrosis, and when arteries are the targets of the microorganisms, arteriosclerotic changes may ensue (Ilback et al., 1990; Nystrom-Rosander et al., 2003). Inflammatory fluid seems to accelerate the uptake of lipoproteins in resident macrophages (Raymond et al., 1985) and the increased uptake of lipids in CBV infection is histologically localised to "macrophage dense" areas (Ilback et al., 1990). Concomitant to the lipid accumulation, there is increased uptake of fat soluble substances, such as TCDD in target organs of infection (Funseth

and Ilback, 1994; Funseth et al 2002). Moreover, an infection-induced decrease in detoxification capacity of xenobiotics may further increase a changed body burden in infected individuals (Funseth et al., 2002a) and explain earlier findings of a decreased elimination of TCDD in mice infected with the parasite *T. spiralis* (Luebke et al., 1994), as well as increased tissue contents of PCB and HCB in *P. berghei* infected mice (Loose et al., 1978). Even if elimination of xenobiotics from blood in infected individuals occurs as in healthy individuals, it is reasonable to assume that chemical substances can remain in infected and damaged tissues for long periods.

12. Interactions between Infection, Nutrients, and Xenobiotics

Several experimental studies with CBV infection have demonstrated that chemical substances (Cd, Ni, Hg and TCDD), even when occurring in small amounts as in food, can produce an aggravated disease, including complications (Funseth et al., 2002b; Ilback et al., 1994a; Ilback et al., 1994b; Ilback et al., 1996). Similar findings have been reported with these and other metals (Pb, Co) in influenza, SFV, VEEV, EMCV, and HSV infections (Burleson et al., 1996; Ellermann-Eriksen et al., 1994; Gainer, 1972; Gupta et al., 2002; Seth et al., 2003). Earlier and higher levels of parasitemia in *T. lewisi* infection have also been detected in animals exposed to Cd, Pb and Hg, than in non-exposed control animals (Hogan and Lee, 1988). Moreover, mice exposed to subclinical doses of PCB (i.e. doses insufficient to produce overt clinical signs of intoxication) showed impaired ability to withstand challenge with *S. typhimurium*, and increased sensitivity to endotoxin (Thomas and Hinsdill, 1978). Similarly, in ducks challenged with duck hepatitis virus doses of PCB, dieldrin, and DDT produced higher mortalities despite no apparent clinical intoxication (Friend and Trainer, 1970). Resistance to the parasite *T. spiralis* has been shown to be decreased after exposure to benzo-a-pyrene (Dean et al., 1982). Prolonged low-dose exposure to bis (tri-n-butyltin) oxide (TBTO), a biocide compound, caused no effects on general toxicologic or basal immunotoxicologic parameters, but decreased resistance to *T. spiralis* as evidenced by increased numbers of muscle larvae and decreased IgE titres (Vos et al., 1984). Moreover, TBTO reduced macrophage function and the clearance of *L. monocytogenes* (Vos et al., 1990). In addition, the severity of malaria (the protozoan infection *P. berghei*) in mice was increased after PCB and HCB exposure, including increased tissue deposits of the xenobiotics (Loose et al., 1978). Thus, even low-dose exposure to xenobiotics without any clinical signs of toxicity or significant immune effects when tested in vitro seems to have the capability to jeopardise the host defence in vivo to a variety of microorganisms. However, an aggravated disease may also indicate an increased toxicity of xenobiotics when exposure occurs during ongoing disease.

Acute infectious diseases in general, regardless of etiology and target organs of microorganisms, are associated with altered dynamics of Fe, Cu, and Zn in the blood (Beisel, 1998; Funseth et al., 2000a; Ilback et al., 2003b). An increased need of trace elements is a general phenomenon in

infection which, for example, results in an increased liver uptake of Zn used for MT synthesis, as well as in redistribution of Fe and Cu (Beisel, 1998; Ilback et al., 2003b; Ilback et al., 2005b). These trace elements are crucial for the host defence (Beisel, 1998; Pekarek and Engelhardt, 1981), including the development of inflammation (Milanino et al., 1993; Pekarek and Engelhardt, 1981). All changes in trace elements, however, may not be favourable for the host (Weiss, 2002), such as the progressive increase of Fe in the brain during scrapie infection in mice (Kim et al., 2000) and in HIV infection in man (Boelaert et al., 1996). Furthermore, many bacteria need Fe for their growth and multiplication and excessive Fe in specific tissues has been shown to promote bacterial infection in those tissues (Al-Younes et al., 2001; Foster et al., 2001; Lounis et al., 2001; Weiss, 2002). Even some neoplasias, cardiomyopathies, and neurodegenerative disorders have been associated with increased levels of Fe (Ke and Qian, 2003; Nystrom-Rosander et al., 2003; Sullivan and Weinberg, 1999; Weinberg, 1999).

Some of the observed changes in tissue trace element levels noted in inflammatory lesions can be the consequence of the associated immunological reaction. This is likely not a complete explanation because the pattern of changes in trace elements in target organs of infection seems to differ substantially in different infections. Interactions between essential (Zn, Fe, Se) and non-essential and potentially toxic trace elements (Cd, Ni, Hg) are well known (Goyer, 1997) and may partly be explained by differences between various infections in their effects on gastrointestinal absorption, blood trace element levels, and target organ uptake and toxicity of essential and non-essential metals.

Cultured macrophages have shown Hg to accumulate, resulting in impaired migration, phagocytosis, and antiviral function (Christensen et al., 1996). Hg has also been shown to impair cytokine production and the respiratory burst of HSV-2 activated macrophages (Ellermann-Eriksen et al., 1994). In target organs of CBV infection and inflammation Hg exposure is associated with disturbed Zn balance (Ilback et al., 2000), as well as more persistent virus, increased inflammation and increased cytokine levels (Ilback et al., 1996). Se interacts with Hg; furthermore it can modify the gastrointestinal uptake and tissue distribution of Hg (Glynn et al., 1993) and potentially limit Hg induced toxicity (Lindh et al., 1996). A concomitant increase in Hg and Se in tissues has been regarded as an inert end-product of the Se-dependent biochemical detoxification of mercury (Bennett et al., 2001). In contrast, the organohalogen compound TCDD is also known to change the trace element balance in infection (Funseth et al., 2002b). Consequently, in the infected host there is reason to suspect that even exposure to low doses of a variety of potentially harmful chemical substances can interact with essential trace elements in different ways. Such interactions, including an effect on the immune system and potentially also on the microorganism, can undoubtedly affect

the course of common infections unfavourably, i.e. the infections will become aggravated with risk for complications.

The effects of Cd on the immune system and host resistance are contradictory. A diminished resistance to EMCV (Gainer, 1977) and an increased amount of HSV-2 in the liver (Christensen et al., 1996) have been reported in Cd-exposed mice. However, in CMV infection there was no effect of Cd on mortality (Daniels et al., 1987), whereas Cd inhalation seems to decrease mortality in influenza-infected mice (Chaumard et al., 1991). This enhanced resistance to influenza infection in Cd-exposed mice was not attributed to an effect on antibodies or IFNs, but due to an enhanced mobilisation of neutrophils and macrophages to the lungs (Chaumard et al., 1991). The brain, as well as the heart, is known to be occasionally a target organ in CBV infection, resulting in meningoencephalitis (Gear, 1984). In CBV infection mortality and inflammatory lesions in the heart were not increased by dietary Cd exposure (Ilback et al., 1994b), but Cd exposure resulted in increased Cu and Fe concentrations in the brain, where Fe was accumulated in focal deposits (Ilback et al., 2005b). Fe accumulation in the brain is also known to occur in HIV patients (Boelaert et al., 1996) and in scrapie-infected animals (Kim et al., 2000).

An infection-associated induction of metal-binding proteins (Funseth et al., 2002a; Ilback et al., 2004) and competition between essential and non-essential trace elements (Goyer, 1997) can account for an unfavourable trace element balance in infected organs (Funseth et al., 2000b; Ilback et al., 2003a; Ilback et al., 2003b; Ilback et al., 2004a). Thus, an infection in an individual exposed to a potentially toxic trace element can result in an increased retention rate of the potentially toxic element during the course of the infection (Glynn et al., 1998; Ilback et al., 1992a; Ilback et al., 1992b), disturbed balance of essential trace elements (Ilback et al., 2000), reduced clearance of microorganisms (Christensen et al., 1996; Ilback et al., 1996; Koller, 1975), changed virulence of microorganisms (Bhaskaram, 2002; Fawl et al., 1996; Thomas et al., 1985), more extensive pathological changes in target organs (Ilback et al., 1994a; Ilback et al., 1996; Seth et al., 2003), and adverse effects on the healing of inflammatory lesions (Milanino et al., 1993). Moreover, during infection, chemical substances have been shown to be redistributed from their normal deposits (e.g. fat tissue for TCDD, liver for Cd) to other target organs that may be more sensitive to toxic insult (e.g., brain for TCDD, kidney for Cd) (Funseth et al., 2000c; Ilback et al., 1993a; Ilback et al., 2004a). An infection may thus result in a different and substance-specific distribution in the body of xenobiotics with new target organs of toxicity.

An infection-induced change in tissue distribution and uptake of potentially toxic trace metals have been shown to change the pathogenesis and increase the severity of several infections (Ilback et al., 1994a; Ilback et al., 1996). In an early study it was shown that even subclinical doses of

Pb increased the mortality in *S. typhimurium*-infected mice (Hemphill et al., 1971), and recently, Pb exposure in SFV-infected mice was found to cause a dose-dependent increase in tissue lesions (Gupta et al., 2002). A striking difference, however, has been noted between Cd and Ni in their effects on host resistance to both CMV and CBV infection, in that mortality is increased by Ni but not by Cd (Ilback et al., 1994a; Ilback et al., 1994b; Selgrade et al., 1992). Moreover, in CBV infection the target organs of toxicity are not the same, i.e. Ni accumulates in the heart, pancreas, and lungs (Ilback et al., 1992a), whereas Cd dose-dependently accumulates in the liver and kidneys (Glynn et al., 1998). The kidney is the critical organ for Cd accumulation and, independent of exposure route, it may cause adverse health effects (e.g., renal dysfunction) (Lu et al., 2001; Nordberg and Nordberg, 2000). The rapid increase in MT in the liver and kidneys during infection may explain an infection-induced flux of both essential (Cu and Zn) and non-essential (Cd) trace elements between organs (Ilbäck et al. 2004), and the previously shown difference in tissue accumulation of Ni and Cd (Glynn et al., 1998; Ilback et al., 1992a; Ilback et al., 1992b). Consequently, infections may well have an impact on the toxicity of metals, unfolding the possibility for detrimental effects even at exposure levels normally regarded as safe.

In mice Se deficiency leads to higher mortality but similar parasitemia of *T. cruzi* causing Chagas' disease (de Souza et al., 2002). Se deficiency may influence the course of Chagas' disease in humans (Rivera et al., 2003). Furthermore, Se deficiency is involved in the pathogenesis of Keshan disease, which is caused by a viral infection (Peng et al., 2000). Both these diseases are associated with inflammatory heart lesions that may result in cardiac insufficiency. Survival in Se-deficient rodents has been reported to be increased in *S. typhimurium*, unchanged in *L. monocytogenes*, and impaired in *S. aureus* and *C. albicans* infections (Ongele et al., 2002). In vitro killing of *S. typhimurium* and *S. aureus* bacteria is unaffected by Se deficiency (Boyne et al., 1986). On the other hand, resistance to *S. typhimurium* and *P. berghei* in rats, and to *P. berghei*, *L. monocytogenes*, and PRV infections in mice seems to increase with Se deficiency (Boyne et al., 1986). Conversely, Se deficiency increases the susceptibility to *S. pneumoniae* infection in mice (Boyne et al., 1986). In vitro tests of function show that Se deficiency impairs the ability of phagocytic neutrophils from rats, cattle, and mice to kill ingested *C. albicans* (Boyne et al., 1986), and down modulation of IL-2 has been noted both in Se-deficient humans and mice (de Souza et al., 2002). Moreover, Se deficiency increases the severity in both influenza (Beck et al., 2001) and CBV infection (Beck et al., 1994), with the latter having been shown to be associated with an increased virulence of the CB viruses (Beck et al., 1994). Conversely, supplementation with Se increases the resistance to CBV infection, which seems to be associated with immune stimulatory effects (Ilback et al., 1998; Ilbäck et al., 1989) and reduced oxidative

stress in the target organs of the infection (Beck and Levander, 2000). Thus, although Se seems to be a more important nutrient in viral than in bacterial infections, it is not yet possible to conclude that a relationship exists between the severity of all viral infections and the Se status. The major beneficial effect of Se may be in limiting tissue lesions that are caused by the infection and, in limiting genetic mutations in replicating viruses.

Today an extensive amount of data is available on the effects of chemical substances on the immune system, but much less is known about the extent to which these changes influence the actual host resistance to infectious diseases. However, in influenza such studies have been carried out. For example, the adaptive immune response to influenza virus is generally suppressed by TCDD, whereas some parts of the innate immune response seem to be enhanced by TCDD (Mitchell and Lawrence, 2003b; Warren et al., 2000; Vorderstrasse et al., 2003). Insufficient ability for cytokine production (e.g. IL-2) in TCDD-exposed mice challenged with influenza virus has been suggested to contribute to the impaired immune (CTL) response, and a more severe disease has been shown to occur in TCDD-exposed mice (Mitchell and Lawrence, 2003b). Mice exposed to as little as 10-100 ngTCDD/kg bodyweight experienced increased mortality in influenza infection (Burleson et al., 1996; House et al., 1990), and in HSV II infection (Clark et al., 1983). This profound sensitivity, however, has not been corroborated in other laboratories where increased mortality is reported to occur in the μg dose-range (Warren et al., 2000). Recently, Nohara et al (Nohara et al., 2002) did not find evidence that oral doses up to 500 ng TCDD/kg compromised host resistance to influenza. Vorderstrasse et al (Vorderstrasse et al., 2003) has concluded that it is unlikely that increased mortality in influenza infection after TCDD exposure results from uncontrolled viral replication because virus titres are not increased and antiviral activity of cytotoxic cells in lungs is unaffected. However, TCDD treatment in mice re-infected with influenza does not affect the ability to clear the virus (Lawrence and Vorderstrasse, 2004). Thus, not unexpectedly, it would seem that TCDD is less deleterious for the outcome of influenza in individuals with some immunity to the virus at the time of a new infection. On the other hand, it is unclear why TCDD-exposed mice show higher mortality in influenza infection because the direct cellular targets for TCDD within the immune system and the stage of the immune activation at which they are impaired have not been clearly defined (Burleson et al., 1996; Lawrence et al., 2000; Lawrence and Vorderstrasse, 2004; Warren et al., 2000).

Constituents in bronchoalveolar lavage fluid implicate pulmonary inflammation as the mode of action in influenza-infected mice (Luebke et al., 2002) and hyperinflammation in the lungs of influenza-infected mice seems to occur from 1 μg TCDD/kg (Nohara et al., 2002; Vorderstrasse et al., 2003). An enhanced neutrophilia in the lungs of TCDD exposed

influenza infected mice seems to be mediated by activation of the aryl hydrocarbon receptor (AhR) and is directly correlated with decreased survival after TCDD exposure (Teske et al., 2005). This underscores the importance of evaluating numerous endpoints when using host resistance models. Only limited information exists regarding TCDD in bacterial and parasitic infections. Thus, TCDD does not affect the susceptibility to *L. monocytogenes* infection in animal experiments (House et al., 1990), though it does reduce immune defence mechanisms against both endotoxin-producing (*S. typhimurium*) and non toxin-producing (*S. pneumoniae*) bacteria (Hinsdill et al., 1980; Thigpen et al., 1975). TCDD also seems to increase intestinal parasite expulsion of *T. spiralis* (Luebke et al., 1994). NK cell activity both in the spleen and blood (Funseth and Ilback, 1992), and blood IFN levels (Funseth et al., 2002b) that are protective in CBV infection (Ilback et al., 1989; Ilback et al., 1993b) seem to increase by TCDD exposure. Even though TCDD had a limiting effect on viral replication and the development of the inflammatory lesions in the heart, mortality was increased (Funseth et al., 2002b). Moreover, PCB-exposed mice show increased mortality to HSV infection, but an unchanged ability to induce IFN (Imanishi et al., 1980).

Several questions therefore remain regarding the mechanisms by which TCDD-treated mice die from various infections. One likely explanation is the toxic effects of TCDD on immune cells and an increase in TCDD toxicity on target organs of the infection where immune cells accumulate, which, in turn, increase the tissue pathology (Vorderstrasse et al., 2003). Furthermore, an increased aggressiveness of the microorganisms as a result of TCDD exposure has been suggested to be contributory (Funseth et al., 2002b). A third possible explanation to the TCDD-enhanced mortality in infected individuals would be toxic effects not directly immune related, but rather the result of a cytokine-governed redistribution of TCDD to sensitive organs as part of the acute phase reaction.

Consequently, the increased lethality caused by TCDD in influenza (Burleson et al., 1996; Lawrence et al., 2000; Warren et al., 2000) and CBV infection (Funseth et al., 2002b), as well as lethality induced by PCB and HCB in parasitic infection (Loose et al., 1978; Luebke et al., 1994), may be associated with tissue accumulation of the xenobiotic. Halogenated aromatic hydrocarbons are able to bind to the specific aryl hydrocarbon receptor (AhR) and thereby act as an inducer of the cytochrome P450 enzyme system (Kerkvliet, 2002), i.e. the detoxification system for a variety of hazardous xenobiotics (Morgan, 1997). Cytokines produced during infection (see acute phase reaction) are important for the regulation of the P450 system (Morgan, 1997; Singh and Renton, 1981). The transcriptional activation of P450 genes (CYP1A1, CYP1A2) by TCDD has been shown to be initiated by IL-1 (Morgan, 1997). Accordingly, in CBV-infected mice TCDD (Funseth and Ilback, 1994; Funseth

et al., 2002a) and PBDE (Darnerud et al., 2005) exhibit changed target organ distribution and an associated decrease in the detoxifying capacity of these xenobiotics (Fig. 8). In addition, TCDD has been suggested to promote excessive inflammation (Vorderstrasse et al., 2003). Thus, a plausible explanation for an increased toxicity of organohalogen compounds in infection, and to a decreased host resistance and

Figur 8 Hepatic CYP1A1 and CYP1A2 activities in control mice and in mice at 3 days after inoculation with CBV (Darnerud et al., 2005)

complications in infections after xenobiotic exposure is a cytokine-induced down-regulation of the detoxifying P450 system (Darnerud et al., 2005; Funseth et al., 2002a; Luebke et al., 1994), concomitant to a redistribution (Funseth et al., 2000c) and increased accumulation of lipids (Ilback et al., 1990) and the lipid-soluble TCDD in target organs of toxicity and infection (Darnerud et al., 2005; Funseth and Ilback, 1994; Luebke et al., 1994). Storage of potential immunotoxic substances in target tissues of infection and inflammation can therefore be assumed to have a considerable impact on the disease process. It may influence virulence and replication of microorganisms, metabolic processes, the function of mobilised immune cells, the repair of tissue lesions and the development of autoimmune reactions that may contribute to a changed pathogenesis in several infections, including CBV infection.

13. Discussion

The ability of a pathogen to cause infection depends on a successful invasion of the host, which, in turn, requires that the host's various defence mechanisms are overcome. For the host, an infectious process is a highly complex situation to deal with, even in situations where the immune system is not disturbed by different toxic chemical substances or in the deficiency of essential nutrients. This is true for all the three phases (the incubation period, the acute phase, and the recovery phase) of a generalized infectious disease (Fig. 3, page 31), and which the host has to successfully control for survival. During each phase, characteristic host responses occur that can be assumed to have various sensitivities to adverse effects of xenobiotics, as well as supportive effects of nutrients. While an effect in any immune function can be potentially deleterious it does not necessarily mean that the host resistance to all or a specific microorganism is adversely affected.

During the incubation period, a chemical substance (Cd, Hg, TCDD) that affects virulence or replication of an organism, the balance of essential trace elements, or the initial immune activation and cytokine production has the potential to cause an early change in the progression of the disease, including changing the target organs of the infection, and/or the severity of the disease. In the acute phase of the disease the same chemical substance may have different effects; for example, it may compete with other essential trace elements, influence other arms of the immune defence, and disturb the production of metal-binding proteins, often resulting in a more severe course of the disease. Furthermore, the tissue uptake of the chemical substance is frequently changed in the acute phase of the disease. This could lead to changed toxicity to the tissues and to interactions in target organs of the infection where microorganisms and toxicants may "cooperate" resulting in increased damage. Finally, in the recovery phase the same chemical may in situ disturb those immune cells and trace elements involved in the clearing of microorganisms and healing of lesions in the target organs of the infection. Consequently, xenobiotics may affect the course of an infectious disease differently depending on in which phase of the disease the exposure occurs. Importantly, the infectious process can decrease the activity of the detoxifying system and thus increase the toxicity of xenobiotics, where xenobiotic exposure can change the target organs of both the infection and the major toxicity. This has never before been discussed in studies of xenobiotics in host resistance models and may explain discrepancies in findings regarding effects on host resistance, course of disease, complications, and changes in pathogenesis.

It is well-known from clinical studies that an impaired metabolism in infection can modulate the P450 system, causing drug toxicity as a result (Morgan, 1997). The increased severity of MCMV infection after exposure to the pesticide parathion was suggested to be due to viral-induced interferon-mediated depression of the P450 system (Selgrade et al., 1984). Although cytokines are important for the regulation of the P450 system, viral, parasitic, and bacterial infections evoke different cytokine patterns (Dyatlov and Lawrence, 2002; Luebke et al., 1994; Warren et al., 2000). It is also clear that the activities or expression of individual P450s may be affected differently by different cytokines (Morgan, 1997). Because they are differently expressed in different organs (e.g., the liver, kidneys, and brain), even the activities of specific P450s may depend on the site of infection. Thus, the detoxification, tissue accumulation, and target organ of toxicity may depend on the type of microorganism and the cytokine pattern it evokes. This is likely part of the explanation for the sometimes conflicting results reported on the toxicity of xenobiotics in infections.

Because neither the amount of virus nor the immune function is appreciably affected (Funseth and Ilback, 1992; Funseth et al., 2002b; Luebke et al., 2002), the increased mortality observed in experimental animals after exposure to TCDD in both influenza and CBV infection (Burlinson et al., 1996; Funseth et al., 2002b) is probably due to an increased toxicity as a result of decreased elimination (Luebke et al., 1994) and the associated tissue accumulation of TCDD (Funseth and Ilback, 1992). Moreover, the down-regulation of the P450 system (Darnerud et al., 2005) coincides with stimulation of the acute phase protein synthesis (such as MT) (Ilback et al., 2004a) and a disturbed balance of essential trace elements in the target organs of infection where TCDD accumulates (Funseth and Ilback, 1994; Funseth et al., 2002b). It is reasonable to assume that a nutritional imbalance, concomitant to an infection-induced down-regulation of the detoxifying capacity and induction of metal-binding proteins, can significantly influence toxicological effects and the development of pathophysiological changes in the host.

In addition to metals and organohalogen compounds exposure even to other exogenous chemicals (e.g., pesticides and aflatoxins) have been suggested to be factors in the pathogenesis of disease. It has been suggested that viral infections through the modulation of cellular xenobiotic-metabolising enzymes may be involved in the handling of environmental carcinogens (Chen and Nirunsuksiri, 1999). Hepatitis B virus (HBV) infection and aflatoxins are risk factors for hepatocellular carcinoma and one hypothesis to this interaction is that carcinogen metabolism is altered in the presence of virus induced liver injury (Chomarat et al., 1998). It seems that the mechanisms for disease development involves the virus antigen and associated liver cell injury and a concomitant induction of carcinogen metabolising enzymes (Chemin et al., 1999).

A more severe EMCV infection has been noted in mice pre-treated with pesticides (Crocker et al., 1986) and pesticide mixtures (DDT, fenitrothion) have been shown to potentiate infection-induced (EMCV) fatty changes in the liver and kidneys, as well as mortality (Crocker et al., 1974). However, subsequent studies on EMC and influenza B in mice indicate that the emulsifier used in pesticide preparations were mainly responsible for the enhancement of virus lethality (Crocker et al., 1986). These surfactants, acting as emulsifiers and wetting agents for chemicals ordinarily not water soluble (e.g., certain pesticides), have also been shown to enhance infectivity of a wide variety of viruses in various mammalian cell lines (Roze et al., 1978; Schmidt, 1983). Thus, surfactants seem to increase the gastrointestinal absorption of chemicals (Ilbäck et al., 2004b) and possibly the sensitivity of cells to microorganisms.

Intestinal homeostasis relies upon the equilibrium between absorption (nutrients, ions), secretion (ions, cytokines, IgA) and barrier capacity (to pathogens and chemical substances) of the digestive epithelium. The gastrointestinal absorption of non-essential and essential trace elements can be modulated by nutrients, such as lipids (Ilbäck et al., 2004b), and other trace elements, such as Se and Cd (Glynn et al., 1993), as well as infection (Glynn et al., 1998). Because of an increased need of trace elements in generalized infections, the trace element balance is changed in the blood and in target tissues of infection (Beisel, 1998; Friman et al., 1982; Ilback et al., 2003b). A changed gastrointestinal uptake in infection seems to be associated with cytokine-mediated effects on the colonic epithelial barrier (Fasano et al., 1991; Roselli et al., 2003; Walsh et al., 2000). Bacterial infection (*S. enteritidis*) increases cytokine mRNA levels in enterocyte-like Caco-2 human intestinal cells, an increase that was further enhanced with higher Fe concentration (Foster et al., 2001). An elevated Fe status is known to increase the susceptibility to various infections (Al-Younes et al., 2001; Foster et al., 2001; Lounis et al., 2001; Weinberg, 1999; Weiss, 2002). Moreover, Fe accumulation in the liver in human hepatitis C virus infection is associated with an impaired response to IFN α therapy and with faster progression of the disease (Weiss, 2002). Colonization of the small intestine by enteric microorganisms, or systemic infection associated with an immune response that also involves the gastrointestinal tract, may lead to a more permeable intestine that permits the passage of macromolecules and antigens that cause immune-mediated pathologic changes in the host. Additional studies are necessary to determine whether an altered intestinal cytokine expression in systemic infections increases the absorption of potentially toxic chemical substances and subsequently the severity of the infection, target organ toxicity, and disease pathogenesis. Excessive uptake through gastrointestinal absorption may explain several findings of an increased toxicity of chemical substances after exposure during infectious diseases.

Many diseases are associated with Fe overload and excess of Fe has been shown to worsen the outcome of a variety of infectious diseases (Lounis et al., 2001; Serafin-Lopez et al., 2004; Weinberg, 1999; Weiss, 2002). Although sites of initial deposition of excessive Fe seem to vary in different infections, adverse consequences on pathogenesis seem to occur. It has been suggested that prevention of Fe loading might beneficially affect complications of HIV infection and perhaps indirectly slow the progression of HIV infection itself (Boelaert et al., 1996). Whether excessive Fe accumulation in target organs of opportunistic infections in HIV and AIDS is the initial event that causes the complications or if it is a consequence of the disease processes, including the host responses associated with infection, is not known.

HIV patients become increasingly immunocompromised, and smoking has been reported to increase the risk for opportunistic infections and reduce the progression time by almost 50% (Boelaert et al., 1996). Smoking provides a chronic inflammatory stimulus to the macrophage population of the lungs (Grimble, 1996); in addition, it increases Cd levels in blood, renal cortex, whole body, and urine (Lu et al., 2001). In several virus infections in mice, including EMCV, SFV, and VEEV, Cd causes an earlier virus attack and more extensive pathological changes in the brain (Seth et al., 2003). Moreover, Cd seems to induce a dose-related increase in the susceptibility to HSV (Thomas et al., 1985) and to accumulate dose-dependently in target organs of infection and toxicity (Glynn et al., 1998). Cd is also known to adversely affect the virulence of several microorganisms and the course of the infection (Chaumard et al., 1991; Seth et al., 2003). It is clear that the impairment in host resistance that is due to deficiency of nutrients (Se, Zn) or exposure to xenobiotics (Cd, Hg, Ni, PCB, and TCDD) to extents that are common in the population can be sufficient to increase the risk for complications that are caused by viral, bacterial, and parasitic infections. It is also clear that the early infection-induced increase in MT causes a redistribution of essential as well non-essential trace elements (Ilback et al., 2004a). An infection-induced induction of metal-binding proteins and the competition between trace elements can account for an altered trace element balance in infected organs, an increased uptake of potentially toxic metals, deficiency of essential trace elements, a change in metabolism and immune functions, and finally in a changed virulence and clearance of the microorganisms. This may be a common situation in many infections that could adversely influence the development and severity of the disease when the host is concomitantly exposed to potentially toxic trace elements, even at levels in the physiological range.

Trace metals provoke a special interest in processes involved in viral replication and immune cell proliferation, i.e. metal ions are essential for the preservation of protein structure and some of the key proteins involved in cell proliferation and/or interactions with DNA having metal-

containing catalytic sites (Fernandez-Pol et al., 2001). In a study on enterovirus infected pigs that showed neurologic signs and mild non-suppurative meningoencephalitis and ganglioneuritis, the clinical signs were not typical to enterovirus infection. This finding was interpreted to mean that As in food had enhanced the pathogenicity of the virus (Pass et al., 1979). However, As has been shown to increase the stability of the replication protein compartments that need to be disrupted for successful replication and production of progeny HSV (Burkham et al., 2001) and to be a potent inhibitor of hepatitis C virus replication (Hwang et al., 2004). Data also show that Ca causes conformation changes in rotaviruses (Pando et al., 2002), Mn causes changes in virulence of HIV (Vartanian et al., 1999), and Cd reactivates latent HSV (Fawl et al., 1996). Moreover, Zn influences gene expression in CMV (Takekoshi et al., 1993) and replication of respiratory syncytical virus (RSV) (Suara and Crowe, 2004). Consequently, in a host of experimental studies several essential (Ca, Cu, Fe, Mn, Se, and Zn) and non-essential (As, Cd, Hg, and Pb) trace elements have been shown to have the capability to influence growth and virulence of various microorganisms (see section "altered virulence of microorganisms caused by nutrients and xenobiotics"). However, different microorganisms seem to have varying requirements of trace elements. The most scaring discovery regarding changes in virulence is in vivo studies in both CBV and influenza showing that dietary Se deficiency can change relatively harmless viruses into virulent forms (Beck et al., 1994; Beck et al., 2001). This warrants further study to determine whether and to what extent it is relevant to humans and other microorganisms. If so, Se-deficient populations may be at increased risk; for instance, at the outbreak of new epidemics expected to appear in the future (Bhaskaram, 2002).

A changed cytokine response to infection in individuals exposed to environmental chemicals may, in addition to an altered immune activation, reflect changes in the release of superoxides and peroxides from macrophages during digestion of microorganisms (Bishayi and Sengupta, 2003; Christensen et al., 1996; Davis et al., 1998). Hg impairs the respiratory burst of HSV-2-activated macrophages (Ellermann-Eriksen et al., 1994) and Pb efficiently blocks murine splenic macrophage nitric oxide production (Tian and Lawrence, 1995). Nitric oxide is highly microbicidal and parasitocidal (Beisel, 1998) and is likely to contribute to phagocytosis and intracellular killing of invading microorganisms (Shankar and Prasad, 1998). TCDD treatment has been shown to suppress influenza-induced cytokine (IL-2, IFN γ) production (Warren et al., 2000) and the level of these cytokines in lymphoid tissues has been suggested to influence the degree to which the immune response (CTL) and host resistance to influenza virus is impaired by TCDD exposure (Mitchell and Lawrence, 2003b). A diminished rate of pathogen clearance in xenobiotic-exposed individuals suggests that the microorganisms may survive in-

tracellularly for prolonged periods, indicating a potential for chronic disease and opportunistic infections (Bishayi and Sengupta, 2003; Hogan and Lee, 1988; Luebke et al., 1994; Sugita-Konishi et al., 2003a; Thomas and Hinsdill, 1978). As a consequence, many of the enhanced toxicological effects of xenobiotics in infection may be related to accumulation of chemicals in the target organs of the infection where they may affect the intracellular killing, growth, and virulence of replicating microorganisms, the inflammatory reaction and the balance of essential nutrients.

Phenotypes of mice with disrupted IFN γ genes show increased susceptibility to many intracellular pathogens, including *L. monocytogenes* and different viruses (Ma et al., 2003). A majority of data supports the notion that Pb impairs host resistance and modifies cytokine production (Gupta et al., 2002). Importantly, animal data on Pb exposure and subsequent virus infection indicate that the immune system responds differently in fetuses of pregnant females who are Pb-exposed during pregnancy (Lee et al., 2002). Accordingly, increased sickness behaviour in *L. monocytogenes*-infected and Pb-exposed young individuals was explained by a differently affected cytokine (IL-1 and IL-6) response (Dyatlov and Lawrence, 2002). It is well recognized that age-dependent changes in immune capacity is important for the host defence system (Luebke et al., 2002).

Children are still growing and they have a larger intake of food relative to their body weight than adults, including potentially toxic chemical substances. If the mother is exposed to low levels of Hg, transfer via the placenta and breast milk occurs that negatively affects the immune system of the offspring rat (Ilback et al., 1991). An infection-induced release of TCDD from fat depots after long-term accumulation may reach blood levels in the mother high enough to be of concern also to the foetus and newborn where the exposure occurs via the placenta and breast milk (Funseth et al., 2000c). Moreover, children are more frequently exposed to respiratory viruses and bacteria than are adults and thus more often infected. Because infants and small children have relatively less muscle protein than older children and adults and thus a very small "bank" of readily available amino acids, the increased need for amino acids during infection for the host defence activation puts these youngsters at a special disadvantage (Beisel, 1998). Therefore, interactions between infections, nutrients, and chemical substances seem particularly important for the fast-growing foetus, the new-born infant, and for children in general. This paves the way for a continual and more extensive life-time uptake and storage of potential noxious chemical substances present in the food and environment.

It is widely known that certain pharmacologically active substances exhibit age-dependent changes in uptake and distribution in the brain (Eriksson, 1997; Ilback and Stalhandske, 2003). During the perinatal period, the brain is particularly sensitive to toxic organohalogen compounds, such as DDT and PCB, which in animal experiments have been

shown to interfere with the development of normal brain function (Eriksson, 1997). Moreover, there is evidence indicating that low doses of such compounds during the early phase of life could lead to increased sensitivity later in life for these and other neurotoxic substances (Eriksson et al., 2000). Potentially, such effects may be further strengthened by an increased uptake of xenobiotics during infections where the detoxifying capacity is decreased and/or the brain is a target organ (Abramsson-Zetterberg et al., 2005; Darnerud et al., 2005; Funseth and Ilback, 1994; Ilback et al., 1992a,b). In addition, the elimination of xenobiotics (e.g., TCDD) seems to be decreased in infection (Funseth et al., 2002a; Luebke et al., 1994) and previously accumulated TCDD can, during the short period of an acute infection, be released in large quantities from its fat depots to be redistributed to target organs of toxicity, such as the brain, which may or may not be a target organ of the infection (Funseth et al., 2000c). Because TCDD seems to promote excessive inflammation (Vorderstrasse et al., 2003) and induce oxidative tissue damage in brain tissues (Hassoun et al., 1998), an infection-induced increase in brain accumulation (Funseth and Ilback, 1994) may have serious implications on brain development and function.

Infections early in life have been suggested to be associated with central nervous system (CNS) malfunctions, including mental retardation (Dyatlov and Lawrence, 2002). The acute phase reaction involves an early increase in cytokine release and production of acute-phase proteins, such as the Cu transporting ceruloplasmin (Beisel, 1998). There is also evidence of ceruloplasmin involvement in the development of Alzheimer's disease (Waggoner et al., 1999) and that absence of functional ceruloplasmin can lead to neurodegenerative disease (Hellman and Gitlin, 2002). The childhood disease Reye's syndrome is characterised by marked brain swelling and fatty change of viscera (Corey et al., 1977). It is usually associated with viral illness, predominantly influenza B or varicella, and ingestion of certain therapeutics and xenobiotic chemicals. Neonates may also acquire transplacental transmission of infection (e.g., *L. monocytogenes*) that results in changed pathogenesis, i.e. meningitis rather than sepsis (Roberts and Wiedmann, 2003). Both lactational exposure of TCDD (Sugita-Konishi et al., 2003a) and neonatal Pb exposure (Dyatlov and Lawrence, 2002) seem to potentiate the disease in *L. monocytogenes*-infected mice. This increased sensitivity was associated with cytokine-mediated processes.

An increase in blood cytokines is a common host response to infections (Ilback et al., 1996; Ilback et al., 1993b; Seth et al., 2003), which seems to involve the CNS (Morris et al., 1997). Although cytokines have a proven effect on the CNS, it is not clear how they act. Certain specific cytokines, such as TNF (Tsao et al., 2001), as well as the induction of inflammatory cytokines with lipopolysaccharide (LPS) (Xaio et al., 2001), change the permeability of the blood-brain barrier. TCDD causes

an increase in the concentration of TNF in the serum of endotoxin-exposed (Taylor et al., 1992) and in influenza-infected mice (Burleson et al., 1996). Further, infections with CBV induce TNF (Ilback et al., 1993b) and this is associated with TCDD accumulation in the brain (Funseth et al., 2000c). TCDD-mediated changes in TNF pathways have been reported to be an important mechanism for enhanced TCDD toxicity (Burleson et al., 1996; Taylor et al., 1992). Moreover, recent data indicate that inflammatory cytokines affect certain metal proteinases, which, in turn, result in weakening, injuries, and disruption of the blood brain barrier (Lukes et al., 1999).

The blood-brain barrier may thus be directly influenced by the microorganisms and/or by the associated immune processes, presumably responding with an increased permeability for both microorganisms and chemical substances. There is some evidence that *L. monocytogenes* can enter nerve endings and then migrate to the brain stem to cause inflammation and CNS infection (Roberts and Wiedmann, 2003). The increase in both Cu and Fe contents in the brain of CBV-infected and Cd-exposed mice may reflect an infection-associated increase in the transport of these elements from the plasma into the brain (Ilbäck et al., 2005b). This notion is in accord with the fact that the meninges and the brain are well-known targets of CBV (Gear, 1984). Likewise, in human HIV infection (Boelaert et al., 1996) and in experimental infection with the neurodegenerative disease scrapie the brain shows increased Fe content (Kim et al., 2000).

Numerous components of the immune system play a coordinated role in fighting infection and alterations in any of these because of xenobiotics or imbalance of essential nutrients may contribute to various changes in host resistance and pathogenesis of the disease. The altered distribution of xenobiotics in infection is, in some respects, specific for each substance, whereas in other respects it seems to be a result of general changes in the metabolism that normally occur during infections. Because each individual is typically exposed to a large number of infections, we can count on the fact that during an individual's lifetime, different vital organs will be "occasional target organs" a considerable number of times for potentially different harmful chemical substances. The results suggest that redistribution of chemical substances is a general phenomenon in infections, regardless of the type of causing microorganism, whereas the target organ can vary with different chemical substances, and to some extent, be influenced by the type of microorganism. What role these "multiple hits" of infections on different organs play in the long run for organ function and the individual's health remains to be solved.

14. Conclusion

The sum of all interactions at the host-pathogen interface, including initiation of the infectious process, propagation of the infectious process, and the mounting of a corresponding host immune response, ultimately determines the outcome of an infection. It is clear that the impairment in host resistance that is due to deficiency of nutrients (Se, Zn) or exposure to xenobiotics (Cd, Hg, Ni, PCB, and TCDD) to extents that are common in the population can be sufficient to increase the risk for complications that are caused by viral, bacterial, and parasitic infections. However, xenobiotics may affect the course of a generalized infectious disease differently depending on in which phase of the disease the exposure occurs, i.e. the incubation period, the acute phase, and the recovery phase.

A few plausible explanations for the mechanisms underlying interactions between infections, nutrients, and xenobiotics are (a) the immune system is affected by the chemical substance in a way that it functions less effectively, resulting in decreased host resistance, (b) the gastrointestinal uptake, the tissue distribution, and metabolism of the chemical substance in the body are altered by the infection, such that the damage to the target organs of the chemical substance increase or even that new organs become the target for toxic insult, and (c) the chemical substance itself affects, alternatively changes, the environment of essential nutrients in such a way that the microorganisms multiply in increasing numbers or that more aggressive mutants get the opportunity to predominate.

The immunotoxic effects of chemical substances have been extensively studied. However, only a limited number of studies have focused on how potentially toxic non-essential trace elements compete with essential elements and affect the immune response, virulence, and apoptosis in the infected host. A clear link between chemical-induced suppression of functional immune endpoints that are associated with the host resistance to a specific microorganism and an unfavourable clinical course has, for a majority of infections, not been established. Moreover, even less is known concerning how nutrients and chemical substances influence the susceptibility to pathogens and the infection-replication phase, as well as how they affect growth and virulence of microorganisms in infected tissues.

It is evident that several xenobiotics unfavourably affect host resistance and the course and pathogenesis of some diseases studied, including CBV and influenza infections. Even the degree of toxic effects, including competition with essential trace elements, as well as the target organ of toxicity seems to be adversely influenced by certain infectious diseases. It is therefore tempting to suggest that the type of microorganism and the

variable intensity of disease, determined by infectious dose and pre-infection level of immunity, governing the strength of cytokine responses affects protein synthesis to corresponding degrees (i.e., induction of our detoxifying system (P450) and metal-binding acute phase proteins) and the trace element balance. An infection-induced decrease in detoxification increases the body burden of xenobiotics and the severity of the disease that, concomitantly to the cytokine-mediated changes in the essential trace elements, may cause an unfavourable deficiency of essential trace elements in target organs of infection and xenobiotic accumulation.

An infection can evidently change the gastrointestinal absorption of nutrients and chemical substances. Besides infection, trace elements and lipids in the food seem to affect the gastrointestinal absorption of xenobiotics. "Abnormal" stimulation of the immune system (mast cells, phagocytes, lymphocytes), caused by an interaction between an infection and xenobiotics, may release inflammatory mediators capable of altering gastrointestinal epithelial function. The gastrointestinal uptake and tissue distribution of chemical substances in healthy individuals are well characterised. However, hitherto studied chemical substances in infection many times show changed and substance-specific distribution, and for some chemical substances there is even accumulation in new target organs involved by the disease. The impact of the infectious process on the intestinal immune system, the gastrointestinal absorption of nutrients and xenobiotics, and interactions between nutrients and xenobiotics during gastrointestinal absorption merits further investigation.

Some chemical substances clearly increase the susceptibility to infectious microorganisms, change the course of the infection and the virulence of the microorganism, resulting in a more severe disease, as well as reactivate resting organisms that normally are present in the body after a primary infection. It is reasonable to assume that infectious microorganisms, at least partly, require the same essential trace elements for their survival and replication as the host. Supplementation with Se and Zn in both experimental and epidemiological studies have a proven beneficial effect on host resistance. However, for several other essential nutrients (e.g., Cu and Fe) more data are required to determine whether supplementation is beneficial or even detrimental for the host in a specific infection. Moreover, xenobiotics, including non-essential trace elements that are potentially toxic to human cells, may also adversely affect microorganism growth and virulence. An unfavourable trace element balance may beneficially affect the growth of a pathogen, increase microorganism virulence, and disturb the healing of infection-induced inflammatory lesions. With an increasing number of emerging pathogens and the increasing resistance of important pathogens to available antibiotics and other medications, nutrients and chemicals are likely to receive increased future attention. Accordingly, there is an urgent need for knowledge how non-

essential and potentially toxic elements interact with essential nutrients in common infections.

The gathered results thus far indicate that an increased health hazard by chemical substances in association with infections can be explained in part by changed disease pathogenesis that is caused by the redistribution and accumulation of chemical substances occurring in the organs of the body involved in the infection, and, in part, by a possibly changed virulence of microorganisms in target organs of infection. In addition, the host nutritional status is crucial for the host defence and the outcome of the disease, as well as for the handling and detoxification of hazardous chemical substances in infection. It seems therefore that even normal and harmless amounts of xenobiotics can constitute a health hazard if, at the time of exposure, the individual carries or is exposed to infection. Furthermore, xenobiotics accumulated during the lifetime of the individual may pose an unrecognised hazard because of the redistribution from depot tissues to sensitive organs that seems to occur for several substances during common infections. Therefore, from a health perspective, in the risk assessment of xenobiotics in our food and environment we need to include synergistic effects between microorganisms, nutrients, and xenobiotics. We should further consider that an unfavourable interaction between infections, nutrients, and xenobiotics in the food and environment may gradually change the illness panorama.

15. Acknowledgements

The critical reading of the text and the valuable comments of Professor Göran Friman are greatly appreciated. Several of the studies cited in this review were supported by funds from the National Food Administration in Sweden, the Swedish Medical Research Council and the Faculty of Medicine at Uppsala University, the Swedish Defence Research and the Swedish Environmental Protection Agency. The work with this review was financially supported by the Nordic Council of Ministers.

Sammanfattning

Interaktioner mellan infektiösa agens, näringsämnen och xenobiotika är ett växande problem när det gäller livsmedelssäkerhet, inklusive livsmedelsburna infektioner. Uppkomsten och förloppet av en infektion bestäms av smittdosens storlek och mikroorganismens aggressivitet (virulens), samt av individens specifika immunitet vid infektionstillfället och immunsystemets effektivitet under pågående infektion. Xenobiotika kan emellertid påverka både vårt infektionsförsvar och virulensen hos mikroorganismer och rubba det normala samspelet mellan värd och mikroorganism. Summan av alla interaktioner mellan värd och mikroorganism är avgörande för hur en infektion utvecklas. En infektion innebär således ett känsligt samspel mellan den infekterade individen och mikroorganismen där båda parter har krav på näringsämnen och där även konkurrens mellan näringsämnen och xenobiotika uppträder. En förändrad balans mellan mikroorganismer, näringsämnen och xenobiotika kan därför påverka både sjukdomsförloppet och toxiciteten av xenobiotika.

Följande bakomliggande mekanismer kan tänkas förklara varför ogynnsamma interaktioner mellan infektioner, näringsämnen och xenobiotika uppträder: (a) immunsystemet påverkas av xenobiotika på ett sätt att det fungerar mindre effektivt och därmed resulterar i ett försämrat infektionsförsvar, (b) upptaget från mag-tarmkanalen, samt distributionen och metabolismen i kroppen av xenobiotika förändras av infektionen på ett sådant sätt att skador i målorgan för xenobiotika ökar, alternativt att nya organ blir måltavla för toxiska effekter, (c) xenobiotika påverkar själva direkt mikroorganismen, alternativt ändrar miljön av essentiella näringsämnen, på ett sådant sätt att tillväxten av mikroorganismer ökar eller att mer aggressiva och patogena mutanter får möjlighet att dominera.

En ökad hälsorisk av xenobiotika i samband med infektioner har i studier visats kunna bero på en förändrad sjukdomspatogenes orsakad av redistribution och ansamling av xenobiotika i främst de organ i kroppen som är involverade i infektionen (infektionens målorgan), dels vid vissa infektioner av en förändrad virulens hos mikroorganismen i infekterade organ. Ett antal xenobiotika har visats öka mottagligheten för infektioner, förändra förloppet av infektionen och virulensen hos mikroorganismen ledande till en svårare sjukdom, samt även reaktivera vilande mikroorganismer som normalt kan kvardröja i kroppen efter en primär infektion. Även lågdos-exponering för xenobiotika där man ej ser några kliniska symptom eller tydliga immuneffekter in vitro har visats kunna påverka infektionsförsvaret in vivo för ett antal olika mikroorganismer. Det har således visats i studier att infektioner kan öka skadligheten av xenobiotika, främst p.g.a. att dessa ämnen under den s.k. akutfasreaktionen redi-

stribueras till nya känsliga organ som hjärta, thymus, hjärna och pancreas. Det återstår att visa huruvida infektionsorsakad skadlig redistribution av xenobiotika även sker vid exponeringsnivåer som normalt anses som säkra.

Den infekterade individens näringsstatus är av central betydelse för infektionsförsvaret och för hur sjukdomen utvecklas, men även för kroppens hantering och avgiftning av potentiellt skadliga xenobiotika under infektionen. De kemiska ämnen man hittills studerat under infektion visar i de flesta fall en förändrad och för varje substans specifik distribution i kroppens olika organ, för vissa xenobiotika sker även upptag i nya organ som är målorgan för den specifika infektionen. En minskad avgiftning ökar kroppsbelastningen av xenobiotika och många gånger även sjukdomsintensiteten. Infektioner leder normalt till en förändrad balans av essentiella spårämnen i kroppen, vilket kan leda till brist av essentiella spårämnen i målorgan för infektionen och även till att upptaget av xenobiotika ökar i dessa organ. En sådan förändring kan stimulera tillväxt och öka virulensen hos mikroorganismen, samt även störa utläkning av infektionsorsakade inflammatoriska vävnadsskador. Upplagring av potentiellt immunotoxiska ämnen i målorgan för infektion och inflammation kan antas avsevärt påverka sjukdomsprocessen. Med ett ökande antal nya patogener och en hos viktiga patogener ökad resistens mot tillgängliga antibiotika och andra läkemedel kan man anta att betydelsen av näringsämnen och kemiska ämnen för mikroorganismtillväxt och virulens kommer att få ett ökat framtida intresse. Det bör således ha hög prioritet att skaffa ökad kunskap hur icke essentiella och potentiellt toxiska ämnen interagerar med essentiella näringsämnen vid vanliga infektioner.

Vissa studier talar för att även normalt harmlösa mängder av xenobiotika kan utgöra en hälsorisk om individen samtidigt bär på eller utsätts för en infektion. Eftersom varje individ normalt utsätts för ett mycket stort antal infektioner, kan man räkna med att olika livsviktiga organ många gånger under livet blir "tillfälliga målorgan" både för infektion och potentiellt skadliga kemiska ämnen. Vilken roll dessa "multiple hits" av olika organ på sikt spelar för organfunktion och individens hälsa återstår att utreda. Dessutom kan en lång tids upplagring av xenobiotika i kroppen utgöra en ökad hälsorisk eftersom det vid infektion sker en nedbrytning av kroppsdepåer och en samtidig frisättning av xenobiotika som kan omfördelas till känsliga organ.

Det är därför viktigt att i ett hälsoperspektiv, vid riskbedömning av xenobiotika i mat och miljö, inkludera synergistiska effekter mellan mikroorganismer, näringsämnen och xenobiotika. Vidare bör beaktas att en ogynnsam samverkan mellan infektioner och kemiska ämnen i mat och miljö kan öppna upp för ett nytt eller förändrat sjukdomspanorama. Rapporten är en översikt av vetenskapliga artiklar och belyser mer specifikt punkterna som mer generellt diskuteras i sammanfattningen.

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