Fever, Pyrogens and Cancer

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The observation, that cancer patients who experienced a feverish period after surgery survived significantly longer than patients without fever, and the fact that spontaneous tumor remission was observed mostly after a fever period, was the rationale for the artificial induction of fever ("fever therapy"). The history and rationale for fever therapy are presented and the immunological basis for endo- and exotoxin-induced tumor regression are discussed on the basis of nearly 800 citations of research literature. The effects and clinical research of different biological inductors of hyperthermia like Coley's Toxin (MBV), Propioni bacteria, Corynebacterium parvum, Bacillus Calmette Guerin (BCG), OK-432, Staphylococcus protein A, and Streptokinase are described. Though the biological effects of fever on tumors are well characterized and interesting biological and immunological results are obtained, and some clinical observational studies and small randomized trials show very promising results, larger controlled GCP-conform trials are still lacking. In combination of moderate and extreme whole body hyperthermia with chemotherapy, radiotherapy or immunotherapy with monoclonal antibodies, significant improvement in outcome of the treatment of cancer patients is to be expected. The toxicities of active "fever therapy" or passive "fever-range whole body hyperthermia" are tolerable.

History and Background

The history of fever therapy begun with the heroic induction of fever in the mid-19th century by the German physicians Busch,[1] Fehleisen,[2] and Richter[3] by subcutaneous injection of toxins from erysipelas to treat cancer patients. The rational for this therapeutic approach was the observation, that cancer patients who experienced a feverish period after surgery survived significantly longer than patients without fever.[4]

The history of Coley's Toxin, a pyrogenic bacterial lysate from *Serratia marcescens* and *Streptococcus pyogenes* began at the turn of the 19th century at Memorial Sloan-Kettering Cancer Center in New York (Coley[5-15]). William B. Coley, M.D., active career 1891-1936 using a bacterial vaccine to treat primarily inoperable sarcoma, accomplished a cure rate greater than 10%. After controlling for lapse time, the time from disease onset until start of treatment with Coley toxins, significantly higher cumulative survival was found for the Coley treatment in three subgroups: (1) Ovarian cancer, distant disease - higher survival in years 2-10 (10 year follow-up); (2) Breast cancer, premenopausal distant disease - higher survival in years 2-3 and 5-8 (8 year follow-up); and (3) breast, post-menopausal regional disease - higher survival in all 5 years of follow-up.

Coley's interest in the subject developed when he lost his first cancer patient, a young girl from the Rockefeller family, with a sarcoma in her right arm. In spite of radical surgery, she later died of metastatic cancer. In the course of his work, the physician noted that patients who developed bacterial infections after sarcoma surgery faired much better than those who did not develop postoperative infections. Specifically, Coley studied the medical records of a patient with four instances of large recurrent inoperable sarcoma of the neck and noted that the patient experienced regression under the influence of *erysipelas* (a superficial streptococcal infection of the skin). To further his research, Coley deliberately injected *erysipelas* into some of his cancer patients. Due to initial complications with the formula, the formula was later changed to a combination of gram-positive heat killed streptococcus plus gram negative heat killed bacteria (*Streptococcus pyogenes* and *Serratia marcescens*) called Coley's Toxins or 'Mixed Bacterial Vaccine' (MBV).

Since then various researchers all over the world have used different bacterial products for the treatment of cancer patients to raise an unspecified immune response in the hope to stimulate humoral and cellular antitumor activities. Later, his daughter Helen Coley Nauts would found the Cancer Research Institute in New York, which has since

pioneered the field. Coley's Toxins, consisting of the two bacteria *Serratia marcescens* and *Streptococcus pyogenes*, have been used in a variety of preparations and indications. They also came known as “fever therapy” or endogenous hyperthermia. Progress in immunology and the discovery of cytokines has led to a better understanding of the mechanisms involved. Coley Toxins and related approaches will be reviewed in respect to the variety of preparations, immunological and clinical results. Coley is credited with pioneering the field of immunotherapy.

In the mid-20th century Issels and Windstoßer continued to treat cancer patients with MBV on an empirical basis.[16] Hager and Abel[17] stimulated in the 1980s the clinical research and therapeutic use and basic and clinical research of endogenous, active hyperthermia (“fever therapy”) with bacterial vaccines (MBV, Vaccineurin) and passive ‘Fever-Range Whole Body Hyperthermia’ (FR-WBH) with infrared radiation by critical analysis and summary of the available literature. Heckel[18] and von Ardenne[672] developed heating devices for passive hyperthermia with infrared radiation.

It has been suggested[19] that an important prerequisition for the successful elicitation of an immunological response and induction of tumor cytotoxicity in the host following bacterial toxin exposure is the preactivation of the host. At Coley's time, this has been the preexposure of large groups of the population to BCG. Importantly, in 1975 the group of Old detected TNF in a BCG-primed mouse. The immunologic preactivation has been confirmed by a large number of in vitro and in vivo studies as an important factor not only in respect to an effective immune response but also for the development of tolerance and toxicity.

Interestingly, the epidemiology of cancer incidence and the incidence of febrile infections have been shown to have an inverse correlation and additionally, spontaneous remissions repeatedly have been reported to be associated with febrile infections (reviewed in ref. [20]). The evidence for these observations will be reviewed.

Rationale

Emerging evidence has developed that cancer is an aberrant regulatory process in which the tumor is in a dynamic disequilibrium with the host. The immunological implications of this evidence are widely accepted in the scientific community but have not found their way into applied clinical practice yet. Immunological functions not only are associated with the expression of oncogenes[21] but also with prognostic factors.[22] Moreover, immunosuppressive factors in cancer patients have been frequently described, as demonstrated by in vitro reactions[23-31] (reviewed in ref. [32]). Additionally, the exposure to endotoxins has been demonstrated to act as a powerful immune enhancer not only in immunocompromised cancer patients but also in other patient groups as demonstrated in numerous studies (i.e., reversal of virally mediated immunosuppression: Friedman et al.[33]).

Furthermore, cytotoxic therapies have been shown to exert often long lasting immunologic depression with the subsequent risk of secondary malignancies.[34-47]

Attempts to reintroduce differentiation and apoptosis is one line of research as has been shown with the successful differentiation therapies in acute promyelocytic leukemia[48] or the clinical reversibility of MALT (gastric lymphomas) after successful eradication of Helicobacter pylori infection.[49] Immunotherapy on the other hand aims to target the body's immune system to attack the cancer cells and has gained popularity as a treatment modality for malignant diseases in the 1960s. A large number of trials, using tumor vaccines, immunopotentiators, interferons, cytokines, and “biological response modifiers”, demonstrated antitumor effects in several malignancies, and, to date, immunotherapy plays a major role in the treatment of advanced renal cell carcinoma and superficial bladder carcinoma. Interferon or interleukin-2, which became available for large-scale clinical trials with the development of bioengineering, however, were shown to be not as effective in human trials as initially expected from animal models. The attempt of unspecific immunotherapy by raising a host response through the application of bacterially derived vaccines is a rational design opposed to the application of single cytokines. Together with our increasing knowledge of the complex immunological network this attempt, based on basic and clinical research should provide progress in treatment of human malignancies.

The rationale for the further study of endo- and exotoxin based cancer therapies will be justified as follows:

1. Established cancer therapy has yet to be improved.[50-52]
2. A new paradigm in cancer treatment is warranted.[53-55]

3. There is an inverse correlation between the incidence of infectious diseases and cancer risk.[20]
4. During and immediately after febrile infections remissions of malignancies have been observed.[20]
5. Pyrogenic substances have been successfully administered in palliative and curative treatment protocols of metastatic cancer
6. Cytokine secretions such as IL-1, IL-6, GM-CSF, G-CSF, IL-12 Interferons, and TNF-a mediate the immunological reactions to the administration of Coley's Toxin. Their induction and the shift from type TH1 to type TH2 cytokines can be individually monitored and the therapy adjusted accordingly. With some exception, i.e., in leukemias, the application of single or combination of cytokines has not contributed to a major breakthrough in the continuing search for a cure for cancer. Otherwise, the imitation of a phylogenetic protection mechanism as old as fever may be safely exploited in association with the powerful diagnostic tools of molecular biology, which may allow the therapist to fine-tune the immunologic response to the given challenge.
7. Side effects of the treatment are manageable.
8. New preparation may be more effective than preparations such as Vaccineurin and Novo-Pyrexal or Picibanil which have been used for this purpose in the past in Europe and Japan, respectively. New preparations are available.[481]
9. The Office of Complementary and Alternative Medicine at the National Institutes of Health in the USA as well the German Ministry for Research list Coley's Toxins as a treatment approach with high priority for research.[56,57]
10. Due to the growth in “publicity” of unconventional cancer treatments, the rigorous scientific evaluation of this treatment approach may serve the public, medical providers and third party payers. More importantly, carefully designed studies according to GLP and GCP will lend credibility to this approach and will promote only the best available treatment and bacterial products and hopefully prevent the exploitation by less scientifically qualified providers. As will be discussed, a close immunologic monitoring of the patient is paramount to prevent enforcement of immunologic blocking mechanisms.
11. This study may add benefits to developing new methods in cancer treatments.

Epidemiology

Incidence of Malignancies and Missing History of Fever

Clinical Oncologists repeatedly report that cancer patients stress in their anamnesis that they were never ill before. As a result of this observation, a number of epidemiological studies have been conducted which shall be briefly reviewed here. Already in 1854 Laurence[4] acknowledges the fact that cancer patients have a “remarkable disease-free history”. Schmidt[58] corroborates these findings in stating an “afebrile diathesis” in the history of cancer patients in a study of 241 subjects followed by Engel[59,60] who compared 300 cancer with 300 noncancer patients. Engels' studies demonstrate a cancer risk for people who never experienced an infectious disease calculated with odds ratio (OR) of 2.5 to 46.2. Sinek[61] finds similar results in 232 cancer patients, which he compared with 2.444 controls.

More recent studies confirm the earlier work: Witzel[62] obtained anamnestic data from 150 cancer patients and 150 controls. In this study cancer patients exhibited significantly less visits to their physicians, had fewer secondary illnesses and fewer in-patient hospital referrals. Also, in the five years preceding the diagnosis only two cancer patients developed fever compared to 20 subjects in the control group. Newhouse et al.[63] found in a study of 300 women with cancer of the ovary amongst sociological factors like fewer marriages, fewer incidences of mumps, measles, or rubella compared to an age-matched control group. Remy et al.[64] found an increased cancer risk with an odds ratio of 2.6 for missing history of infectious organ diseases, 5.7 for missing history of common colds, and 15.1 for missing history of fever. Grufferman et al.[65] studied environmental factors in the etiology of rhabdomyosarcoma in childhood. It is the only paper that finds an insignificant correlation with fewer immunizations and a higher rate of preventable infections associated with cancer risk. Rønne[66] could associate a missing history of measles in childhood with increased cancer risk for a variety of tumors in a historical prospective study. Out of 353 individuals with a negative history of measles 21 developed cancer versus only 1 case out of 230 controls with a positive history of

measles ($p < 0.001$).

Van Steensel-Moll et al.[67] reported evidence of a lower frequency of infections in the first year of life for children with leukemia; in this register-based case-control study, common colds, periods of fever, and primary childhood infections showed relative risks (RR) of 0.8, 0.9, and 0.8, respectively. The authors argue that stimulation of the immune system in early life may play a protective role in the development of leukemia. Chilvers et al.[68] performed a retrospective study in which not the absence of fever or infectious diseases but the absence of common cold or a positive history of allergies was tested for their impact on cancer risk. In this study for missing history of common cold and positive history of allergies, no association with increased cancer risk could be established. Remy et al.,[64] Abel et al.,[69-71] and Schlehofer et al.[72] contradicted this study. Abel et al.[70] established in case-control studies with 255 cancer patients compared with 230 controls the highest risk for patients with a low “Infection-Index”. Schlehofer et al.[72] investigated in a population-based, case-control study the medical risk factors of 226 patients with primary brain tumors and 418 controls. She stated a decreased RR for the development of brain tumors for those individuals who had had allergic diseases (RR 0.7; 95% confidence interval (CI) 0.5 to 1.0), diabetes (RR 0.7; 95% CI 0.3 to 1.8), and infections and cold (RR 0.3; 95% CI 0.1 to 0.8). Melanoma patients had fewer atopic symptoms than subjects did in the control group (p less than 0.05). Grossarth-Maticek et al.[73] performed a ten-year prospective cohort study of 1353 persons. He concludes “episodes of high fever during the entire lifespan in the case of an acute illness as a typical reaction are inversely related to later cancer incidence when the subjective reporting of fever is accepted as valid evidence”. Kölmel and Compagnone[74] investigated the role of fever and atopy among melanoma patients. There were fewer feverish infections, while patients with atopy had more feverish complications of their symptoms. Finally, Kölmel et al.[75] demonstrated at 271 controls versus 139 melanoma patients an inverse relation between number of febrile infections and incidence of malignant melanoma.

The correlation between missing history of fever and cancer risk could not be confirmed for acute adult leukemia and ALL in a recent study by Cooper et al.[76] The data of 624 patients with acute myeloid leukemia, 124 patients with acute lymphoblastic leukemia (AML) matched with 637 healthy population controls did not support a protective effect from antigenic stimulation in relation to the risk for acute leukemia in adults.

While discussing the incidence of malignancies and missing history of fever the same question can be asked in relation to immunosuppressive drugs. There is considerable evidence that there is a higher cancer rate after the introduction of immunosuppressive methods accompanying transplantation surgery (Cole[46,47]). Data for increased incidence of neoplasms following therapeutic immunosuppression exist for lung carcinoma,[77] lymphoma,[78-80] bladder tumors,[81] next to several reviews on miscellaneous tumors.[82-86] These data deserve further studies. Possible mechanisms for increased incidence of malignancies have not been elucidated yet and there consists even a controversy whether immunosuppressive or immunostimulatory events are mediating increased carcinogenesis. Furthermore the immunosuppressive effects of chemotherapy are well known and there has been association between chemotherapy and secondary malignancies.[33-35,37-39,44]

Spontaneous Remissions and Feverish Infections

It is of obvious interest for this review to analyze the literature on reports of spontaneous remissions in cancer following infections with or without fever. O'Regan and Hirshberg[87] give an extensive overview of the field. The older literature consists mainly of the reports of Coley, meticulously documented in eighteen monographs mainly by his daughter Helen Coley Nauts.[88-109]

Analysis of the literature[87] reveals leukemia with ≥22% being the magnitude of cases where infection was associated with remission, followed by bone and connective tissue cancers with ≥15%, melanoma with ≥11% and lymphoma with ≥7%. Spontaneous tumor remissions during or following feverish infections have been reported already in the beginning 19th century (Vautier,[110] see Nowotny[111]). There are several older reviews[112-115] which report spontaneous remissions next to more recent studies by Everson and Cole,[116-119] Stephenson et al,[120] Cole,[121,122] Nauts.[102] Remissions of leukemia following systemic infections have been noted throughout the century.[123-125] Stephenson et al[120] reported in their analysis that an infection or persistent fever preceded 224 cases of spontaneous remissions. Additionally, febrile infections have been shown to increase the survival expectancy of cancer patients.[126-130] Nowacki and Szymendera[131] state a highly unfavorable prognostic significance for postoperative fever and/or septic complications in colorectal cancer patients. Fucini et al[132] disagree with this statement and show in a retrospective

analysis no significant prognostic influence of postoperative fever and/or septic complications in this patient group.

Treon and Broitman[133] described post-transfusional hepatitis as a common complication in patients with acute myelogenous leukemia (AML) which "paradoxically" prolonged survival. They identified the impaired hepatic endotoxin (LPS) clearance in patients with acute viral hepatitis as the reason for endotoxemia and elevated TNF-α release, a mechanism referred to as endothelial translocation (see: Translocation). They also observed virally induced IFN-γ secretion, which in turn acts in synergy with TNF-α anti-proliferative and as a mechanism inducing differentiation. Finally, in a recent monograph on spontaneous remissions of malignant melanoma Maurer and Kölmel[134] list 21 cases of the world literature, where febrile infections have been associated with spontaneous regression of metastatic melanoma. These authors state further "the connection of febrile infection and tumor regression is the most frequent association found in the literature".

The following list contains the described and additional references in most of which spontaneous infection and/or fever had been associated to remission of neoplastic disease. Some articles refer to assumed mechanisms of spontaneous regression and some articles are review papers.

Spontaneous Remission Listed Under Tumor Types

(Please see Table 1)

Fever and the Immune Response

Fever as the imminent sign of infectious diseases has been used as a diagnostic indicator since ancient times.[233] It is one of the oldest nonspecific responses to infection, both in vertebrates and invertebrates.[234] Temperature rise during fever establishes a cascade of host defense mechanisms that increases host survival and induces T cell proliferation and differentiation, secretion of interferons (IFNs), antibodies and neutrophil migration.[235,236] Fever as a part of the acute-phase reaction and the role of cytokines in thermoregulation have been reviewed recently by Dinarello.[237,238]

The interest in fever as a therapeutic tool is dating back to Parmenides (ca. 540-480 B.C.) who stated: "Give me the power to induce fever and I will cure all diseases". And in the seventeenth century the English physician Sydenham (1624-1689) described the reaction of the organism to pyrogenic substances: "Fever is a mighty engine, which nature brings into the world for the conquest of her enemies". Ever since Burnet[239,240] has postulated his theory of immunological surveillance and the first limitations of aggressive cancer treatments became obvious, research has focussed on the possible role of the immune system in cancer incidence and prognosis. As it has been shown and will be discussed further fever, as an innate and phylogenetic very old mechanism, deserves the best of our scientific attention as a powerful tool in the ongoing search for the cure of cancer.

Cytokine research has elucidated the immunological response underlying fever. Direct primary endogenous pyrogens are IL-1alpha, IL-1beta, TNF-alpha, TNF-beta (lymphotoxin-alpha), IL-6, macrophage inflammatory protein 1, and IFN-alpha.[239,241] Indirect inducers are considered to be IL-2 and IFN-gamma.[238] Exogenous pyrogens are considered to be the lipopolysaccharides of the cell wall of gram-negative bacteria such as *Serratia marcescens* and the exotoxins of gram-positive bacteria such as streptococcus and staphylococcus, which are also called bacterial superantigens. Fever-induced temperature changes have been shown to augment immunological defense mechanisms in vivo and in vitro.[234,235,242-246] Increased temperatures stimulate the proliferation but not cytotoxicity of cytotoxic T lymphocytes (CTL) which then can perform their effector function at all physiological temperatures in the body.[247-249] It has been shown that binding of bivalent antibody can neutralize picornaviruses by irreversibly neutralizing the virus at temperatures that are higher than physiological by disrupting the virion, leading to ejection of the RNA. Fever enhances this process in vivo, confirming the popular belief in the virtues of fever.[250] Not all researchers report enhancement of immunity: Incubating temperatures of 39° C have been shown to suppress natural killer cell activity in vitro in the presence of IL-1 or interferon-alpha.[250] But the immunological effects are not only depending on temperature but also on time (Figs. 1, 2, 3, 4, 5, 6, 7).

Glucocorticoids inhibit various components of the acute phase response, particularly the increase in body temperature induced by endotoxins. Endogenous glucocorticoids function as part of an inhibitory feedback system involved in the modulation of fever by decreasing plasma IL-6, CSF, PGE2, and PGF2 alpha concentrations.[251]

The Immunological Basis of Endo- and Exotoxin-induced Tumor Regression

The Shwartzman Phenomenon

The Phenomenon of Local Skin Reactivity to Various Microorganisms

Shwartzman[252] was the first to describe the phenomenon of local tissue reactivity, later referred as the Shwartzman phenomenon (SP). Because of the importance to the subject it shall be briefly described here:

Shwartzman injected a single intradermal cultural filtrate from *B. typhosus* free of exotoxins into rabbits, which was followed 24 hours later by a single intravenous injection of the same filtrate. Only four hours after the intravenous injection Shwartzman observed severe hemorrhagic necrosis at the site of skin injection. Furthermore it was shown that the second dose of the filtrate had to be given intravenously since repeated intradermal injections did not elicit the SP. Interestingly the SP induced cross-reactivity since it could also be provoked when using intravenous injections from filtrates derived from biologically and serologically unrelated microorganisms. These included *Meningococcus, B. typhosus, B. paratyphosus, B. coli, b. friedlaender, B. dysenteriae, B. prodigiosus* (later known as *Serratia marcescens*), *B. lepisepticus, B. pestis, B. influenza, B. pertussis*, and *Vibrio cholera*. Additionally *Ascaris lumbricoidis* elicited the SP whereas yeast, ricin and diphtheria toxin did not show strong responses. The same phenomenon of different bacterial species sharing similar mechanisms of sensitization has been observed for the induction of endotoxin tolerance, as will be described below.

Timing played a crucial role. The appropriate time between the initial skin injection and the subsequent intravenous injection for the intravenous injection ranged from eight to thirty-two hours after initial skin injection with an optimum incubation period of twenty-four hours. Outside this range no SP could be elicited.

The pretreatment of a large amount of different microorganisms revealed considerable heat resistance which, though, differed widely between different strains and even within the same strain.

Shwartzman observed fluctuations of the potency of various preparations in refrigerated storage. There was increase as well as decrease of potency upon storage of several months. It was hypothesized that fluctuations in potency of filtrates are accompanied by the formation of “toxoids”, which retain their power to combine with neutralizing antibodies.

Interestingly, SP could be elicited in rabbits, guinea pigs, goats, and horses but not in mice and rats. But, as will be discussed later, murine animals bearing sarcoma, again showed a marked SP in their tumor. Later, it became clear that interferon-gamma (IFN-gamma) plays a critical role in eliciting the SP, since monoclonal antibodies to IFN-gamma could completely prevent the SP. Also, IFN-alpha and IFN-beta had a desensitizing effect.[253]

Reactivity of Malignant Neoplasms to the Phenomenon of Local Skin Reactivity

Applying the same technique of sensitizing animals with intradermal injections of bacterial filtrates Shwartzman observed upon subsequent intravenous injection of bacterial filtrates into tumor bearing animals severe hemorrhagic necrosis and remissions of tumors. This observation referred to transplantable and spontaneous tumors.

Comments on the antagonism between tuberculosis,[254] malaria and tick fever[255] and the development of carcinoma built the early epidemiological hypothesis about the protective mechanism of infections against cancer. Gratia and Linz[256] continued Coley's early work in liposarcoma-bearing guinea pigs by combined intratumoral and intraperitoneal injection of *B. coli*. Instead of the skin these animals were sensitized directly at the tumor site. In later experiments the authors only choose the intraperitoneal route without previous injection at the skin site and still could elicit severe hemorrhagic necrosis of tumors. No hemorrhagic lesions were observed in other visceral sites.

While the SP in nontumor bearing animals was restricted to nonmurine species, tumor-bearing rats and mice showed a marked SP in their tumors. Mouse sarcoma 180 inoculated by Shwartzman and Michailovsky[257] were treated with intravenous injection of *Meningococcus 44B*. Hemorrhagic tumor necrosis and complete regression of tumors were observed in mice receiving repeated intravenous and intraperitoneal injection of the bacterial filtrate as early as one hour later.

Further experiments revealed “positively (1) and negatively (2) reacting tumors”:

1. Positively responding tumors were sarcoma S/37, sarcoma 180, adenosarcoma M/63, Twort adenocarcinoma and Walker sarcoma. While “…very young, perfectly healthy tumors often gave no reaction, larger tumors gave

practically 100 per cent positive results".[253] This observation is in consistency with the literature which postulates the necessity of an immune response to develop gradually as noted later by Berendt,[200,201,258] and described by Wiemann and Starnes[19] as window in time. Obviously immunity can not be developed in hosts bearing very young tumors.

2. Negatively responding tumors were not further specified slow growing spontaneous or transplantable malignant tumors, which rarely or never regress, heterologous grafts of rapidly growing malignant tumors, which eventually regress, and benign, rapidly developing granulomas or embryomas, which eventually regress. Already in his time Shwartzman hypothesizes that the newly formed and highly fragile tumor vessels may have been one of the target mechanisms of endotoxin induced tumor necrosis. This observation is most interesting in the era of substances blocking VEGF and other mechanisms of nevascularization.

Shear[259] performed experiments with 2000 mice. He produced profound hemorrhagic necrosis and in some cases complete regression of malignant tumors following intravenous administration of *Meningococcus*. It further can be stated from this work and the experiments of Shwartzman and his contemporaries, that there is a direct correlation between the ability of a filtrate from a given microorganism to prevent the development of sarcoma 180 in mice and to elicit the SP in rabbits.

Much later, in 1985 Aoki and Mori[260] described a local SP (LSP) confined to the tumor and a generalized SP (GSP) spreading to different visceral sites such as kidneys, liver, spleen and lung. Using E. coli endotoxin in Vx-2 carcinoma bearing cottontail rabbits they produced a GSP additionally to the hemorrhagic necrosis of tumors (LSP). The proposed mechanism of action for this phenomenon is disseminated intravascular coagulation (DIC), resulting in fulminate hepatitis and other organ changes. While GSP and DIC have not routinely been observed in patients undergoing mixed bacterial vaccine therapy for immunotherapy of cancer, those observations are important to keep in mind.

Reflections on Immunotherapy of Cancer with Bacterial Lipopolysaccharide (LPS)

Gratia and Linz[257] showed in guinea pigs the hemorrhagic necrosis of transplanted liposarcoma if the animals were treated with E. coli filtrates. Shwartzman and Michailovsky[258] treating mice with the Sarcoma 180 with parenteral application of *Meningococcus* culture filtrates observed hemorrhagic tumor necrosis and eventually complete remissions. Shear after isolating an endotoxin later defined as LPS as the active component of gramnegative bacteria,[261] subsequently induced necrosis in primary and experimental tumors.[262] The discovery of LPS as the active compound of bacterial filtrates led to efforts to isolate and synthesize LPS. The group of Westphal at the Max Planck Institute in Freiburg pioneered this field (for a review see ref. 263). The endotoxin-induced necrosis is being initiated rather quickly: 4-8 hours following exposure to endotoxin the tumor tissue becomes inflamed; after additional 10-20 hours the center of the tumor necrotises.[264] Additionally, numerous endotoxin induced effects upon the immune system have been observed: Stimulation of the reticulo-endothelial system (RES), activation of macrophages,[265] stimulation of B cell mitogenity,[266,267] increased antibody synthesis,[268,269] induction of interferons, fever, leukopenia followed by leukocytosis. (For reviews of molecular mechanisms, see i.e.: refs. 270-275). It also should be mentioned that in vitro macrophage responsiveness to endotoxin does not necessarily indicate high in vivo sensitivity to endotoxin challenge.[276]

The immunological response to exposure of a variety of viruses and lipopolysaccharides (endotoxins) has been clearly corresponding with antineoplastic effects.[19,133,200,201,263,277-289] Moore et al[290] showed that post-endotoxin sera (*C. parvum* and *S. abortus* equi-Novo Pyrexal) contain high levels of myeloid colony-stimulating factor(s) (GM-CSF) and factors capable of inducing terminal granulocyte and macrophage differentiation of the murine myelomonocytic leukemic cell line WEHI-3. Also, exposure to endotoxins at work has been associated with decreased cancer risk.[291]

Kearney and Harrop[292,293] argue that exposure to endotoxin might enhance tumor growth. They legitimately point to the importance of excluding endotoxin from solutions used in studies of experimental tumors. Other authors fear exposure to infections may lead to a process labeled "inflammatory oncotaxis".[294-297] Recently, this phenomenon has been described further by researchers identifying cytokines, leucocytes and macrophages in long standing cancers as promoters of tumor growth.[298,299] These infiltrations are being compared to chronic infections whereas the attempt to induce an immune response to cancer by artificially induced fever may be compared to an acute phase reaction observed in acute infections. The literature discussed in this review does not lend itself to suggest enhancement of

tumor growth following antigenic exposure to spontaneous occurring tumors in human and animal models.

Chun and Hoffmann[279] reported that application of low doses of LPS could substantially increase the efficacy of TNF against murine cancers. What might be even more important is their observation that the blockage of two negative feedback responses occurring as a response to LPS treatment, namely the production of prostaglandin E (PGE_2) and the generation of $CD8^+$ suppressor T-lymphocytes ($CD3^+$ CD16/56-), dramatically increases the ability of mice to reject tumor transplants. In humans Otto et al[289] achieved only one complete remission (CR) with intravenous endotoxins from *Salmonella abortus equi* in 27 patients with colorectal (1 CR, 2 PR) and 15 patients with nonsmall cell lung cancer (NR). While this group clearly could not come close to the results achieved by Coley, the group has performed numerous studies with the same strain of Salmonella[278,282-288] (see: Salmonella abortus equi).

Morita et al[300] achieved dose-dependent inhibition of tumor growth with a synthetic lipid A analogue in a hamster pancreatic carcinoma model. Interestingly, endogenous tumor necrosis factor (TNF) activities were significantly greater in tumor than in serum, spleen and liver. Another group did not observe any antitumor effects with an isolated lipid A from Salmonella typhimurium and Salmonella Minnesota.[301] TNF production by macrophages stimulated with lipid A after culture was much greater when the culture was performed in the presence of hamster pancreatic carcinoma cells (no cell-to-cell contact). Anti-TNF neutralizing antibodies inhibited the cytotoxic activity of TNF secreted by macrophages. The authors hypothesize that lipid A displays antitumor effects by stimulating production of endogenous TNF in tumor macrophages, through activation and production of soluble macrophage-stimulating factors in cancer cells.

Goto et al[302] administered LPS intradermally in animal and human tumor models together with Cyclophosphamide, known for it's synergistic effect with LPS (prostaglandins). After completion of dose escalation, the treatment was continued for at least 4 months, and it was found that 1800 ng/kg LPS was well tolerated. A significant level of cytokines was observed in the sera for at least 8 h. These results indicate higher tolerable doses and remarkably more continuous induction of the cytokines than were reported in a previous study by others using intravenous administration. Three of the five evaluable tumors showed a significant response to therapy.

Jimbo et al[303] showed that intravenous administration of a synthetic lipid A derivative significantly inhibited the growth of transplanted tumors in the liver of rabbits. These results suggest that systemic administration of lipid A induced selective tumor microcirculatory blood flow reduction via local endogenous TNF production. In contrast, local administration of human recombinant TNF alpha through the hepatic artery induced blood flow reduction not only in the tumor region but also in nontumorous liver tissue.

Nowicki et al[304] treated C57Bl/6 mice bearing transplantable Lewis lung cancer (nonmetastatic subline) implanted either subcutaneously or intraperitoneally with macrophage colony stimulating factor (M-CSF), Escherichia coli lipopolysaccharide or both. LPS administered daily once a day for up to 30 days impaired both subcutaneous and intraperitoneal tumor growth and prolonged survival of tumor bearing mice. Macrophage colony stimulating factor administered daily, inhibited only subcutaneous tumor growth, both when administered alone and in combination with lipopolysaccharide, and had no effect on intraperitoneal tumors. Moreover, it did not prolong survival of tumor bearing mice, when administered alone, and nullified the effects of lipopolysaccharide when administered concomitantly. These data suggest that macrophage colony-stimulating factor, at least in this tumor model and in this dose schedule, offers little benefit. In contrast, the present data confirm earlier suggestions on the therapeutic usefulness of bacterial lipopolysaccharides in neoplastic disease.

It has to be noted that hemorrhagic necrosis of tumors is to be distinguished from tumor regression.[305] Endotoxin-induced tumor necrosis takes place in the center of solid tumors, often leaving a ring of viable tumor cells behind which eventually will lead to further cancer progression. Endotoxin-induced hemorrhagic necrosis always precedes tumor regression but is by itself only rarely followed by complete regression, i.e., tumor necrosis and tumor regression are mechanistically two separate events. It further has been shown that endotoxin-induced tumor regression requires a state of T cell mediated immune response that is only induced in response to immunogenic tumors as classically defined.[19,200,201] Human tumor rejection antigens, which are recognized by T cells, may play an important role in the unspecific as well as specific immunotherapy for cancer.[306-310] The hemorrhagic necrosis is thought to create conditions within the tumor, that are facilitating the entry and functioning of effector T cells, an observation in accordance with the abilities of endo- and exotoxins to induce the expression of cell adhesion molecules[311-314] and of TNF to induce capillary leaks.[315-318] This T cell response again needs as an activation signal a prestimulation with

antigenic substances such as BCG, corynebacterium parvum[319,320] or the tumor antigens itself.[200] The prestimulation has been associated with a highly activated macrophage system, which elicits the release of TNF and plays an important role in removing tumor cell debris.

It is important to realize that the acquisition of concomitant immunity precedes endotoxin susceptibility. This process is generated over time following successive tumor growth and has been described as “window in time” when mice become susceptible to subsequent endotoxin challenge.[19]

In summary the following endogenous mediators have been identified which are relevant to endotoxin-induced tumor necrosis: TNF, IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, granulocyte-macrophage differentiation factor (GM-DF), colony-stimulating-factor-1 (CSF-1), granulocyte-macrophage (GM-CSF), granulocyte-stimulating-factor (G-CSF), interferon-beta, and interferon-gamma (for a review see ref. 321). Moreover, the IL-12 mediated balance between TH1 and TH2 cytokines on the one hand and the functional balance between prostaglandins and IL-1 mediated effects on the other side determines the type of immune response. Structural requirements of endotoxic reactions can be summarized as follows. (1) Lipid A structures proved to be the carrier of the toxic properties of endotoxin. (2) Conversely, beneficial reactions can be initiated not only by the complete structures but also by structural remains, which are no longer toxic. (3) Some of the split products in the lipid-free and polysaccharide-rich preparations can induce beneficial reactions. (4) Gram-negative bacteria can produce endotoxin-unrelated and beneficial compounds. Conventional endotoxin preparations are heterogeneous and often contain some of these unrelated substances.

Coley Toxins Used in the Treatment of Cancer

Helen Coley Nauts, in an admirable effort, has compiled the work of her father William B. Coley in numerous articles and 18 monographs (Nauts HC: Monographs #87-108). The following critical points shall be mentioned from the analysis of Helen Coley Nauts work:

Variability of the Preparations Used

For the period between 1891 and 1953 Nauts reported the use of 14 different preparations of Coley toxins (Nauts[105]): (see Table 2).

The variability of the preparations used makes it desirable to determine which preparation reveals the biggest benefit in which cancer type. The importance of this fact has been stressed by Nowotny et al.[272,322] Also, it is important to know which cytokine pattern is being induced by various techniques of growth and preparation. This research has been taking place in the nineties at the laboratories of Memorial Sloan-Kettering Cancer Center (personal communication: Nauts 1997) and awaits publication.

Mikolasek[323] demonstrated rejection of tumor allografts in mice treated with enzymes of (grampositive) *Streptococcus pyogenes* (streptolysine, streptokinase, streptodornase and hyaluronidase). He observed high antistreptolysine (ASLO) titers in the serum of mice and strong inhibition of subcutaneously implanted cystic adenocarcinoma following exposure to antigens. In addition, the author describes a complete spontaneous remission of a human adenocarcinoma of the uterus surviving 19 years since a Wertheim operation. Interestingly, this patient had had a high ASLO titer (595 IU/ml serum) which leads the author to speculate that an intercurrent *Streptococcus pyogenes* infection had taken place resulting in functional mitral valve impairment and induction of immunity against metastatic disease. Although, as it is pointed out, the mouse tumor was allogenic and human tumors are autologous, the association between his observations appears to be valid. It might be interesting to look at epidemiological and clinical data to compare cancer incidence and ASLO titers in humans.

Techniques and Timing of Administration

Site and dosage of application of the Toxins are of considerable interest. Whereas Coley choose the intratumoral approach in his early years beginning in 1892 it was not until 1925 that Coley used the intravenous approach, which elicited stronger febrile reactions with smaller dosages. He also used intramuscular and subcutaneous administration, some of which have been questioned to be effective due to poor resorption.[103] It might be advisable to test small amounts of the toxins subcutaneously to rule out hypersensitivity reactions (personal observation). Of special interest is the intraperitoneal application since several cases of dramatic tumor regression in ovarian cancer have been reported following this route of administration.[105] Application other than the intravenous route bears the advantage of slower

release of endotoxins and more continuous stimulation of the host immune system.[105]

Frequency and duration of injections of Coley Toxins obviously play another crucial part in the outcome of therapy. Daily or every other day injections often produced the best results.[105] However, the general condition of the patient, compliance issues, the phenomenon of tolerance (see: Tolerance) and hypersensitivity (see: Toxicity) suggest at least a 48-hour interval between injections. Coley suggested a six-month period during which treatment should be continued often performed by the attending family physician even after remission might have occurred. Only in later years Coley[14] attributed treatment failures after initial tumor regression to a too early stop of therapy.[105,108]

Recent experiments confirm the importance of timing of toxine administration in experimental animal models.[324] In this study it appeared that early intravesical BCG toxine therapy of bladder tumors, initiated after tumor inoculation resulted in slower progression rate than treatment initiation after a longer waiting period. Moreover, single injections of endotoxins in tumor bearing animals have been shown to induce periodically changing periods of enhanced beneficial effects, followed by phases of responsiveness below normal towards the immunological challenge.[325] Further Nowotny et al[272] recently showed that the time intervals between endotoxin treatment and tumor challenge are of utmost importance to the capability of animals to reject a subsequent tumor challenge. While previous experiments used allogenic tumors and the elicited immune response was based on allogenic recognition and destruction of these tumors,[326] in this study endotoxin-induced rejection of less immunogenic tumors also was shown to be possible. However, there was a small time frame (-5 days until +1 days) when endotoxin inoculation elicited protection against subsequent tumor challenge. Later inoculation did not protect animals and higher doses even showed reduced immunity against leukemia L1210 cells. Conclusions from these observations for the therapy of established syngeneic tumors only can be speculative.

Stage of Disease

The inverse relation between tumor load and immunological function is well established. [327,328] Chasseing et al[329] could demonstrate that the immunosuppression associated with later stages of tumor development might be due to direct effects on monocytes, by down regulating IL-1 production. Also, in this study an increase in the levels of prostaglandin E2 and serum immune complexes could be detected. Related studies of the prognostic significance of circulating immune complexes (CIC) in malignant tumours of head and neck revealed a correlation between the level of CIC and stage of disease in head and neck cancer patients: Seropositivity for CIC increased quantitatively with stage of disease.[330] However, CIC containing MUC-1 encoded polymorphic epithelial mucin (PEM.CIC) was decreased in advanced breast cancer, i.e., there was an inverse correlation between positivity for PEM.CIC and extent of disease.[331] Mucins, encoded by the MUC1 gene, and CD43 (leukosialin) as the core protein, secreted or expressed in the plasma membrane of cancer cells could interfere with NK cell-mediated lysis in a dose-response-dependent way.[332] The CTL response against differentiation antigens of the melanocyte lineage correlated inversely with antigen expression (Melan A/MART-1).[333] Here, metastases increasing in size over time showed a loss of Melan A/MART-1 expression in the presence of CTL.

Studies on natural killer (NK) cell activity showed a significantly lower cytotoxic activity in patients with laryngeal carcinoma who had histologically confirmed nodal involvement.[334] The study of serum immunoglobulins correlated with tumor load, while the estimation of CIC and blocking effect of cancer sera on normal lymphocytes was of diagnostic and prognostic significance.[335] Wiltschke et al[21] showed reduced mitogenic stimulation of peripheral blood mononuclear cells as a prognostic parameter for the course of breast cancer in correlation to tumor size and axillary lymph node involvement. Thus, it is desirable to decrease the tumor burden prior to initiation of immunological therapies. If this attempt includes the use of chemotherapy, treatment related changes in the phenotype of target cells should be considered.[336-340]

Radiation and Toxin Therapy

Before the era of chemotherapy started in the 1950, irradiation was the treatment of choice for many inoperable tumors. The review of Coley's work shows that a large number of his patients received concomitant radiation therapy.[97,100-105,107,108] Already in 1942 Shoulders[341] noted beneficial effects by combining the toxin therapy with irradiation in a series of far-advanced malignancies. Interestingly, toxins protected animals from otherwise lethal total body irradiation.[342] Donaldson et al[343] observed the effect of Coley's Toxins and irradiation on the A. melanoma # 3 tumor in the golden hamster. She concludes: (1) toxin therapy does not affect survival; (2) toxin pretreatment

potentiates X-ray therapy; (3) metastases are not affected; (4) normal tissues do not show increased radiosensitivity; (5) toxins plus X-ray therapy do not affect the prognosis or survival of the host; (6) toxins plus X-ray therapy show a synergistic effect". Nauts several times points to the radiation-sensitizing effect of the toxins while normal tissue was better protected from side effects of radiation. Chandler[344] achieved beneficial results in six out of eight patients with rhabdomyosarcoma, melanoma, and sarcoma. These tumors were usually considered radio resistant. The radioprotective effect later has been described by Behling and Nowotny,[324] and Nowotny.[270,345]

Tang et al[346] used Mixed Bacterial Vaccine (MBV) in the multi-modality treatment of hepatocellular carcinoma (HCC). Patients undergoing palliative resection and cisplatin therapy and radiotherapy, which were randomized to receive MBV, had an improved one and two year survival. In addition, MBV improved the "second look" resection rate to 40% as compared to 17% in the control. MBV could also prevent decrease of macrophage activity caused by radiotherapy.

Kempin et al[182,183] demonstrated improved remission rate and duration in nodular non-Hodgkin lymphoma (NNHL) and advanced Nodular Lymphoma (NL) with the use of mixed bacterial vaccine (MBV) in combination with radiotherapy.

Other Toxins, Bacterial and Viral Products Used in the Treatment of Cancer

Toxins and bacterial products in the treatment of cancer shall only be briefly mentioned because it would be beyond the scope of this review, which shall mostly focus on Coley toxins (for reviews see refs. 347-354).

Bacillus Calmette Guerin

Old et al[355] were the first to report upon beneficial effects of treating tumor bearing mice with Bacillus Calmette-Guerin in the USA. Howard et al[356] confirmed earlier studies of the effect of BCG infection on the sensitization of mice to bacterial endotoxin and *Salmonella enteritidis* infection. They found that mice infected two weeks previously with BCG were extremely susceptible to the lethal action of endotoxin. On the other hand mice were more resistant than normal to infection with *Salmonella enteritidis*. Without BCG administration the phenomenon of endotoxin tolerance would have occurred (discussed under: Tolerance). Ruddle and Waksman[357] demonstrated increased lymphocytic cytotoxicity after sensitization with tuberculoprotein. Schwartz et al[194] inhibited murine sarcoma virus oncogenesis with living BCG. Bluming and Ziegler[143] and Mastrangelo[358] successfully treated melanoma patients but observed different immunological effects of BCG depending on the route of administration. Hakim[359,360] points to the possibility of enhanced tumor growth by BCG; he assumes that the serum from BCG-treated sarcoma-bearing animals blocks the spleen lymphocyte-mediated cytotoxic activities directed against proliferation and growth of the sarcoma. Remissions of skin melanoma metastases following BCG injection have been shown by Remy et al.[198] Vosika[361] gives a comprehensive review of clinical immunotherapy trials of bacterial components derived from Mycobacteria and Nocardia: Preparations of isolated mycobacterial cell wall or cell wall skeleton attached to oil or to trehalose dimycolate have been favored over crude extracts and caused regression of disease and established tumor-specific immunity.

Hence, BCG has been approved for the treatment of superficial bladder cancer.[362-364] Recently upregulation of Inter-celluar-cell-adhesion-molecule-1 (ICAM-1) expression as an important mechanism of action of this treatment has been described on bladder tumours.[310,311] The ICAM-1 – CD11a pathway can render bladder tumour cells vulnerable to nonantigen specific cytotoxicity mediated by activated lymphocytes. Recent results of local BCG treatment for T1 G3 bladder cancer, after TUR-B, showed a reduced risk of recurrence and mortality.[288] Conti et al[288] and Jackson et al[365] could further show that BCG potentiates monocyte responses to lipopolysaccharide-induced tumor necrosis factor, soluble tumour necrosis factor receptors and interleukin-1, but not interleukin-6 in bladder cancer patients. Also, exposure to BCG has been shown to enhance interleukin-8 release in macrophages, a major inflammatory cytokine associated with enhancement of the immune response.[366] It should be mentioned here that the group of Old discovered TNF in a BCG primed mouse.[319]

Propioni Bacteria

Propioni Bacteria (PB) (Synonym: *Corynebacterium parvum*) (CP) are amongst the potent immunomodulators stimulating cell populations involved in nonspecific resistance. Generally, the activated immune system provides

protection from infectious pathogens and malignancies via mechanisms of recognition and elimination. Accordingly, administration of Propionibacteria could be shown to be of benefit in the treatment of neoplastic and infectious diseases. Thus, it may be recommended for further clinical investigations (for reviews see refs. 367-369).

In vitro research showed induction of lymphokine-activated killer (LAK)-like cells capable of killing both natural killer (NK)-sensitive and NK-resistant tumor cells as well as syngeneic macrophages (M phi) (Chen et al[370]). Anti-interleukin-2 (IL-2) or anti-interferon (IFN) alpha, beta antibody significantly inhibited this induction of LAK-like activity by CP, suggesting that the generation of killer cells by CP was dependent on IL-2 and IFN(s) produced in the culture.

Bursuker et al[371] showed, in accordance with Keller et al,[372] that CP could render a murine nonimmunogenic tumor (M109) immunogenic. This immunity was tumor-specific and T-cell-dependent. T cells from mice whose progressive M109 tumors had been excised were capable, on passive transfer, of inhibiting adoptive immunotherapy of T-cell-deficient recipients by spleen cells from mice immunized with an admixture of M109 cells and CP. The authors argue, that the lack of anti-tumor immunity in this tumor model was not due to the absence of tumor-associated antigens but, instead, due to a shift of the balance from effector and suppressor arms of the immune response. Shifting the balance in favor of the effector arm by means of CP resulted in a measurable immune response to a nonimmunogenic tumor.

Karashima et al[373] showed that modification of NK cell activity is a possible basis for modulation of anti-metastatic activity by CP. Administration of CP showed a biphasic change in NK activity of the spleen cells and the peritoneal exsudate cells (PEC) in mice. Initially after administration of CP, the NK activity of the spleen cells and PEC was significantly augmented. At a later phase (14 days) after CP administration, the NK activity was deeply depressed.

Further animal experiments with *Propionibacterium acnes*-metabolites revealed stimulation of proliferation, maturation and emigration of thymocytes and lymphocytes,[374] and inhibition of experimental lung metastasis of murine sarcoma L-1 in BALB/c-mice.[375] Pulverer et al[376] further demonstrated a protective effect of combined treatment (CP and liver lectin blocking by D-galactose administration) on the liver colonization of RAW 117-H10 lymphosarcoma in BALB/c-mice. Both, immunomodulation with CP as well as liver lectin blocking by D-galactose treatment significantly decreased the number of liver tumor colonies in this experimental model. The authors favor the combination of CP and D-galactose, which proved superior to each monotherapy since the liver colonization by RAW 117-H 10 lymphosarcoma could be completely inhibited.

Lipton et al[377] demonstrated CP versus BCG as adjuvant immunotherapy of stage II malignant melanoma as superior over BCG when measuring disease-free and survival times. Foresti[378] showed beneficial results in treating malignant pleural effusions with intrapleural instillations of CP. Of 20 patients with malignant pleural effusions (MPE) treated with intrapleural CP, 18 (90%) had a CR and 2 patients (10%) had a PR. Preoperative immunostimulation by *Propionibacterium granulosum* KP-45 in colorectal cancer resulted in resistance to the spread of cancer during operation.[379] In this study PB was administered intravenously between the seventh and third day prior to surgical treatment for colorectal cancer. For stage I carcinoma the survival rates, were 91% in the treated and 63% in the control group respectively. For stage II carcinoma the survival rate was 90% for the treated group with distant spread in 1 case and 45% in the control group where the rate of recurrence was 55%. For stages III and IV there was no statistically significant difference in survival between the treated and the control groups. Raica[380] studied 96 patients with superficial bladder tumors treated by transurethral resection in order to investigate the value of intravesical CP to prevent recurrences. Patients were studied in a 3-year follow-up. Recurrences were observed in 21.1% of cases in the CP treated group and in 54.5% of cases in the untreated group. Chronic lymphocyte infiltrates appeared to be the mediating event for the action of CP as an adjuvant therapy in urinary bladder cancer. These observations are in contrast with the recently elucidated tumor growth promotion by immune components;[298,299] thus the stage of the disease may be a critical factor since intravesical tumor cells only would recur in situ.

Salmonella Abortus Equi

Salmonella abortus equi has been studied for its antineoplastic effect by many authors in murine and human models[278,282-291] (for reviews see refs. 263,275,321,381). Lipid A as the active compound has been isolated from the cell wall of *Salmonella abortus equi*.[278,382,383]

The isolated product was known in Germany as Novo-Pyrexal. Engelhardt et al[281] determined dose-limiting toxicities including chills and fever (WHO grade III) following intravenous application at 1.0 ng/kg of body weight (maximal

tolerated dose-1, MTD-1). The interesting finding was that endotoxin could be administered intravenously using 4,0 ng/kg body weight when the patient was protected by 1,600 mg ibuprofen. The induction of high amounts of circulating tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), interleukin-8 (IL-8), granulocyte colony-stimulating factor (G-CSF), and macrophage colony-stimulating factor (M-CSF) was not influenced by ibuprofen administration. Conversely, repeated injections of LPS at daily intervals resulted in marked downregulation of the cytokine induction (see: Tolerance) with the exception of IL-1 beta and G-CSF.[287] Interestingly, cancer patients pretreated with 50 µg Interferon-γ 12 hours prior to endotoxin administration exhibited not only prevention of downregulation of endogenous cytokines (IL-6, IL-8, G-CSF, TNF alpha) normally observed after repeated endotoxin application, but showed enhanced secretion of these cytokines to levels even higher than those achieved after the first LPS challenge.[284] As mentioned earlier, only moderate antitumor activity was observed in different trials.[283,284,286,287,290] Further results of studies with *Salmonella abortus equi* will be discussed in the cytokine and tolerance section of this paper.

OK-432

OK-432 is the benzylpenicillin-treated lyophilized powder of *Streptococcus pyogenes* group A cell wall extract. The product is known in Japan as Picibanil, Chugai Pharmaceutical Company, Tokyo, Japan. The TNF inducing properties of OK-432 are well known[384] (for reviews see: refs. 385-392). OK-432 has been widely tested in at least 18 randomized clinical trials. Caution in regard to validity and generalizability of these trials are indicated in reference to several aspect according to Abel:[389] "(1) the overwhelming majority of trials has been conducted in the same geographical region, Japan; (2) the intention to treat was violated in most studies; (3) case numbers in most studies were very small; (4) careful statistical analysis revealed a null hypothesis in most studies; (5) randomization was conducted by the participating clinicians".

Nonetheless, the antitumor effects of the substance are well established and warrant further careful designed prospective, randomized studies. Studies have been performed for cervical cancer,[393-395] bladder cancer,[396,397] gastric carcinoma,[398-405] lung cancer,[406-410] liver cancer,[411,412] malignant gliomas,[413] chylothorax following esophageal cancer.[414]

In basic research and animal models Nio et al[415] demonstrated antitumor activity of orally administered OK-432 on murine solid tumors. Noda et al[416] induced Interferon-gamma in human peripheral blood mononuclear cells by OK-432. Sekimoto et al[417] showed the production of TNF by monocytes from cancer patients and healthy subjects induced by OK-432 in vitro, and its augmentation by human interferon gamma. OK-432 activated mononuclear cells were shown to be able to kill T98G glioblastoma cells by apoptotic mechanism through the Fas ligand/Fas system.[418] Moreover, it has been demonstrated that the intrapleural administration of OK-432 in 70-80% of patients with malignant pleural effusion from metastatic lung cancer stimulated clinical improvement but more importantly, mediated a reduced suppressor macrophages and increased NK cell activity and cytokine production such as IL-1, MCF by macrophages and IL-2 and NK cytotoxicity factor by lymphocytes.[419,420] These authors achieved similar results earlier in patients suffering from cancer of the stomach or the lung.[421]

Proteolytic Enzymes with Special Reference to Streptokinase

Streptokinase is one of the active enzymes of the streptococcus strain used by William B. Coley and has a long history in cancer research ever since. Additionally, streptokinase has become an important tool in measuring plasminogen activation.[422] However, there are scientists who think of streptokinase and other proteolytic enzymes to augment metastasis and others, who think of those enzymes as a promising adjuvant in cancer therapy. Both lines of thinking shall be briefly elucidated.

While the external use of (proteolytic) enzymes in preclinical and clinical research has been long a domain of substituting genetically deficient enzymes (reviewed in: ref. 423), considerable evidence is mounting for their usefulness in a variety of immunologically mediated diseases including cancer and there has been increasing interest in the clinical use of proteolytic enzymes.[424,425] Clinical trials have examined the therapeutic efficacy of both single and combined application of these enzymes in individuals with a number of different conditions, including trauma, inflammatory and autoimmune diseases, mastopathy and cancer.[424,428]

The fact that tumors show enhanced fibrin deposits especially in the invasive periphery has been noted as early as

1958[426] and has subsequently been used for targeting porphyrins as photosensitizers to tumor cells.[427] Hence, the well known fibrinolytic effects of proteolytic enzymes have been suggested as a therapeutic rationale in tumor therapy. Additionally, numerous additional molecular mechanisms in support of this rationale have been elucidated lately.

There is an increasing body of knowledge for the immunological mechanisms underlying the effects following exposure to proteolytic enzymes in vivo and in vitro. (For brief comments on the rationale of therapeutic use of proteolytic enzymes, see refs. 428,429). As for the oral forms of proteolytic enzymes their enteric resorption as biologically intact macromolecules has been described.[424,430-432]

Already more than 20 years ago rejection of tumor allografts following treatment with enzymes from *streptococcus pyogenes* was demonstrated by Mikolasek,[433] activation of cellular immunity in cancer patients and enhanced activity of E rosette forming lymphocytes following proteolysis in vitro by Holland et al[434] and Thornes.[435] These authors described anergic states in cancer patients, which were reversed by administration of proteolytic enzymes. Conversion back to an anergic state after stop of therapy however, resulted in recurrence of the disease. Later, Tomar et al[436] reported activation of NK cells in vitro by streptokinase. (See discussion of the observations by Mikolasek[323] also in C.1 of this review). Additionally, successful therapy of accessible tumors like basal cell carcinomas, mycosis fungoides, and cutaneous metastasis of breast cancer have been reported by local application of streptokinase-dornase.[437]

Alteration of CAM expression has been described recently[438,439] and may be one underlying mechanism for clinical effects of application of proteolytic enzymes. Recently, enzyme-induced upregulation of lymphocyte beta$_2$ integrins, and downregulation of L-selectin and CD44 has been observed in vitro,[440] which may explain some of the immunologically mediated anti-tumor effects of proteolytic enzymes.[423,441-444] NK cells utilize these beta2 integrins (CD11/CD18) for firm binding to tumor target cells,[445-447] and this class of cell adhesion molecules becomes rapidly increased on human NK cells upon activation.[448] Furthermore, cytotoxicity of lymphocytes against tumor cells has been shown to be greatly inhibited when lymphocytes were treated with anti- CD11a and anti- CD18, but not when treated with anti- VLA-4 antibodies.[449] Moreover, decreased CD11a/CD18 cell surface expression has been shown to correlate with a decrease in NK cell activity,[450] and an increase in CD11b/CD18 expression has been shown to enhance adherence of neutrophils to tumor cells.[451]

Additional clinical relevance for cancer therapy might be provided by these studies, which showed reduced expression of CD44 following enzyme treatment. High levels of CD44 expression on cancer cells facilitate malignant cell adherence to the extracellular matrix and thus are promoting metastatic tumor growth.[452,453] Compatible with this observation, an antimetastatic effect of in vivo application of bromelain[441,442] and of streptokinase[454,455] was observed in mice. It is well known that arresting tumor cell emboli in the microcirculation facilitates the development of blood borne metastases. Hence, additionally to the effects on cell adhesion molecule expression, it has been suggested, that enzyme-induced increased fibrinolysis caused a decrease in metastatic seeding. Uster et al[444] showed bromelain to be effective in decreasing the attachment of human bladder and melanoma cells to extracellular matrix components. In this respect it is also of interest to note that the fibrinolytic system in aged rats, and its reactivity to endotoxin and cytokines shows significant decrease in activity which makes the individual more susceptible to endotoxin-induced effects, including microthrombosis and platelet aggregation.[456]

Consistent with these observations is also a study by Murthy et al[457] who demonstrated a decreased tumor formation of TA3Ha mammary tumor cells in healing hepatic wounds of syngeneic strain A mice following treatment with human plasmin B-chain-streptokinase complex (B-SK) and recombinant tissue plasminogen activator (PA). Urokinase and heparin had no effect upon tumor formation in this model. PA was suggested to produce plasmin which, in turn, digests cell adhesion molecule protein structures and in due course inhibits tumor cell attachment. Similar studies of the inhibitory effects of orally and systemically applied proteolytic enzymes on cancer growth and metastasis have been performed by Maruyama et al[458] on sarcoma-180 ascites cells in vivo and by Thornes[459] in clinical studies of postmenopausal patients with breast cancer and colorectal carcinoma. Thornes[435,459] provided evidence that streptokinase treatment attenuated lymphocyte depletion following surgery and increased cellular immune functions. Szreder[460,461] demonstrated remissions of different cancer types in humans and animals following artificially induced abacterial erysipelas and chronic aseptic abscesses.

L-asparaginase has been proven to be a useful adjunct in the treatment of acute lymphoblastic leukemia, but additional experience also suggests a role in acute nonlymphoblastic leukemia.[422] Higher levels of plasma fibronectin in patients

with acute myeloid leukemias and blast crisis have been reported to decrease following streptokinase therapy.[462] Earlier studies, which included streptokinase in an attempt to increase the response to chemotherapy with cyclophosphamide did not show a beneficial effect of the enzyme treatment in that model,[463,464] reported no increased effectiveness of electromagnetic radiation by the use of a single intravenous application of 350,000 IU of streptokinase.

The other line of evidence is concerned with possible enhancement of tumor growth and metastasis induced by administration of proteolytic enzymes. Teuscher and Pester[465] i.e., showed in an in vitro model that the application of antifibrinolytic drugs mediated the inhibition of vascularization of tumors. These authors hypothesized that inhibitors of serine proteinases and of plasminogen activators reduced the migratory behavior of tumor cells and that streptokinase, conversely stimulated cell migration. An earlier study reported increased spontaneous pulmonary metastasis in rabbits following treatment with human serum plus streptokinase, an effect, which these authors attributed to fibrinolysis.[466] McKinna and Rowbotham[467] reported intravascular dissemination following streptokinase injection in an in vitro tumor colon cancer model.

Staphylococcus Protein A

The antitumor property of Staphylococcus protein A (PA) is well documented in the literature in various transplantable murine tumor models (reviewed in refs. 328,468,469). Protein A (PA) is an immunostimulating glycoprotein (mol. wt. 43,000 kDa) obtained from *Staphylococcus aureus* cowan I and attaches to the Fc fragment of IgG 1, 2 and 4, and preferentially binds to IgG included in immune complexes. Plasma absorption over PA has been shown to effectively reduce high levels of pathologic soluble circulating immune complexes (CIC), a method which has considerable less side effects and toxicity opposed to plasmapheresis.

Animal and some human studies showed encouraging results in increasing cellular immunity, reduction in blocking activities and tumor regression with the use of plasma absorption over PA and direct administration of PA.[470-473] Interestingly, some of these authors later reported that a leakage of bacterial products from staphylococcus species during plasmapheresis resulted in a general and unspecific immunostimulation and partially explained the beneficial effects of plasma absorption over PA.[474] Additionally, similar results have been observed when PA has been injected directly into tumor bearing animals.[475,476] It is of interest to note that this approach did not elicit generalized toxicity. Also, PA injection has been shown to suppress the onset of tumorigenesis by inhibiting initiation and promotion of carcinogenesis.[477,478] The indirect action by which PA may foster immunity and reduce CIC has been expressed by Zaidi et al.[479] They suggest that the PA-induced depletion of B-lymphocytes leads to a decreased production of antibodies and subsequently reduced levels of soluble immunosuppressive CIC.

Furthermore, PA has been shown to exhibit potent cytokine stimulating properties and to enhance LAK cell induction and activity in lymphocytes from healthy volunteers and melanoma patients.[480] These studies recently led to the promising application of superantigen staphylococcal enterotoxin A (SEA) combined with the Fab fragment of a tumor-specific antibody[308] as efficient immunotherapy for lung melanoma micrometastasis[309] and lymphoma therapy[307] in mice.

A new development for the administration of a staphylococcus derived enterotoxin has been investigated in China recently. Researchers in China found that the Highly Agglutinative Staphylocoin (HAS), a super antigen biological product made by Shenyang-based Xiehe Group in China known as *Gaojusheng*, can activate the patient's T-cells and repair damaged tissues by promoting or stabilizing the interaction between antigen-presenting cells and T cells.[481] It has been demonstrated that there is a clear relationship between the affinity of Superantigens for the T-Cell Receptor and their biological activity.[482] Xiehe Group had put the super-antigen products into preclinical research in 1989 when the theory of super-antigen was proposed. In Western countries, super-antigen based research was first reported in 1997 for phase I clinical trials.

Other Toxins

Cholera toxin has been shown to effectively inhibit mammary cancer growth in vivo and in vitro.[483] This rejection has been associated with an increase in intracellular cyclic adenosine3”:5”-monophosphate.

Freund's adjuvant has a long history in active specific and nonspecific immunotherapy in cancer and is beyond the scope of this review to be discussed. NK-cell reactivity, i.e., in stage I and II nonsmall-cell lung carcinoma receiving

adjuvant immunotherapy with Freund's adjuvant after surgery, was increased nonspecifically as demonstrated by Maroun et al.[484]

Keyhole limpet hemocyanin (KLH) is derived from an inedible mollusk found on the pacific coast. Immunotherapy with ganglioside-KLH has been performed mainly in superficial bladder cancer and malignant melanoma next to BCG (for reviews see refs. 485,486,487). Gangliosides, containing glycosphingolipids that are anchored into the lipid bilayer of the plasma membrane, and which are overexpressed on tissues of neuroectodermal origin can be targets for the KLH-therapy of melanomas, sarcomas, neuroblastomas and astrocytomas. KLH acts as a potent vaccine targeted at these gangliosides to induce cytotoxic IgM antibodies, which are able to initiate complement mediated cytotoxicity. Intralesional KLH significantly reduced tumor incidence, growth rate, and mortality in the mouse bladder tumor model (MBT2).[488] Moreover, instillation of KLH into the bladder has been found to have fewer side effects than BCG.[489] It has been suggested that a local cytokine release of IL-2, IFNs, and TNF is involved in the effector pathway of KLH application. Sargent and Williams[490] suggest that the lack of endogenous cytokine activity secondary to immunosuppressive events following cancer growth may be overcome by direct, local application of KLH. Interestingly, prevention of bladder recurrence correlated significantly with cutaneous delayed type hypersensitivity testing.[491]

Viral Approaches

There is an extensive literature on the use of viral approaches for the treatment of cancer (for reviews see refs. 492-499). First reports of leukemia treatments with viruses date back to mid sixties[500,501] of the 20th century. Wheelock and Dingle achieved febrile responses to repeated administration of six different viruses and observed clinical and hematological improvement in a patient suffering from AML. Importantly, in this patient, each treatment was followed by significant temperature surges.

Recombinant viral protein derived vaccines for specific immunotherapy of cancer aim at the attempt to specifically target a T cell mediated immune response to cancer antigens. The vaccines are used to enhance the immunogenicity of cancer antigens. The lysis of carcinoma cells by T cells ($CD8^+$ and or $CD4^+/CD8^+$) was shown to be HLA restricted. Incorporating virus in autologous tumor vaccines has enhanced the antigenicity of tumor vaccines. Among viral treatments the Newcastle Disease virus (NDV) has most widely been used as a crude agent as well as using viral vectors.[493,502,503] The Newcastle Disease virus has been shown to be superior in preventing side effects over BCG admixed tumor vaccines.[504] Antigenic targets include normal antigens that have a limited health-tissue distribution or expression (i.e., carcinoembryogenic antigen), viral proteins (i.e., E6 protein of human papillomavirus), and mutated oncogens. Recent research has focused on peptide recognition by cytotoxic T-cells, the expression of antigenic peptides bound to major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells, and the requirement for a second signal for T cell activation, such as the costimulatory molecule B7. It has been shown that viruses attached to autologous tumor vaccines deliver these costimulatory signals to tumor-reactive T cells following postoperative vaccination of tumor bearing hosts.[505]

Viral oncolysates induce two different types of immune response. NK cells induce target cell lysis primarily by the production of granzymes and poreforming proteins and do not need help from memory cells. In contrast, T cells lyse target cells primarily by the MHC-restricted release of lymphotoxin (TNF beta) causing programmed cell death (apoptosis) through endonuclease activation and target cell DNA fragmentation, a process which needs the assistance of memory cells.[498] Shillitoe et al[496] used human papillomaviruses for gene therapy of cancer to target antisense or ribozyme molecules directed against these genes. The viruses are present in many cervical and oral cancers, and are likely to be etiological agents of the tumor. Recently Hodge et al[506] could show that the combination of a recombinant vaccinia virus containing the gene for the costimulatory molecule B7 and a recombinant vaccinia virus containing a tumor-associated antigen gene resulted in enhanced specific T-cell responses and antitumor immunity.

Lately, defective presentation of MHC class I restricted antigens on a murine sarcoma have been identified by the failure of these tumor cells to present influenza virus antigen to virus-specific cytotoxic T cells.[507] This approach in the future could lead to ex vivo assessment of immunogenicity of tumors. Otherwise, it should be considered that MHC class I antigen defective cells are more likely to be detected by Natural Killer cells.[508-514]

Proposed Mechanism of Action

Shear et al[262] discovered in Coley's mixed bacterial vaccine (MBV) lipopolysaccharides (LPS) as the active substances. LPS, which are potent pyrogens, are the component of the outer membrane of gram-negative bacteria. Endotoxins do not kill tumor cells in vitro and therefore their antineoplastic effects have to be mediated by host-dependent mechanisms. These immunologic mechanisms include the activation of macrophages, natural killer cell (NK) (CD3-CD16/56$^+$), cytotoxic T cells (CD3$^+$ CD16/56$^-$) and the release of cytokines.[515]

The prominent cytokines being secreted by activated macrophages and the RES are interleukin 1 (IL-1), interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF α), IL-12, GM-CSF and additionally TNF β (Lymphotoxin).[516,517]

LPS Binding Sites

At least five signal transducing binding sites expressed on the lymphocyte plasma membranes have been identified as LPS receptors including two proteins of 70-80 kDa and of 30-40 kDa, CD14, the CD11/18 family of adhesins and the 95 kDa scavenger receptor.[518-523] The predominant discussed molecule in the literature is a circulating molecule named lipopolysaccharide binding protein (LBP) which forms a complex with endotoxins and was first thought to bind as a complex to the monocyte differentiation antigen, CD14.[518,524-529] Binding of the complex to monocytes and macrophages activates the cytokine secretion cascade of these cells.

Lately it could be demonstrated that the picture is more complex. The LPS receptor CD14 is a protein expressed on the surface of monocytes, macrophages, and polymorphonuclear leukocytes and a soluble, circulating protein in the blood. Both forms of CD14 partake in the LPS response. Studies with recombinant LBP (rLBP) suggested that LBP functions catalytically, as a lipid transfer protein function basically to accelerate the binding of LPS to CD14. On the other hand LPS and rsCD14 complexes formed in the absence of LBP stimulate integrin function on PMN and expression of E-selectin on endothelial cells, indicating that LBP is not necessary for CD14-dependent stimulation of cells.[530]

Recently a novel receptor for *Escherichia coli* heat-stable enterotoxin (ST) has been identified as a highly selective biomarker for metastatic colon cancer.[531-533] ST-receptor interaction was coupled to activation of guanylyl cyclase C (GCC) in all normal tissue samples of colon and rectum and all primary and metastatic colorectal tumors examined. However, neither ST binding nor ST activation of GCC was detected in any extraintestinal tissues examined. It may be hypothesized that these receptors may serve as a target for directing therapeutic administrations of bacterial vaccines to GCC expressing tumors in vivo.

Furthermore, intracellular binding sites have been identified recently at microtubule proteins.[534] This binding site is shared with the microtubule acting agent taxol.[535] Microtubules are constructed from the heterodimers of alpha- and beta-tubulin along with microtubule-associated protein-2. They are mediating mitosis and protein trafficking.[536,537]

Cell Adhesion

The upregulation of cell adhesion molecules (CAM) following exposure to inflammatory cytokines and lipopolysaccharides has been established on a variety of cell types like endothelial cells, fibroblasts, synoviocytes, Langerhans cells, melanocytes, keratinocytes, mast cells, monocytes and eosinophils.[538-545] CAM play a crucial role in endo-and enterotoxin-mediated lymphocyte distribution and target signaling. Alterations in the expression of CAM may have a profound impact on a wide range of immunologic processes (reviewed in: refs. 566,563). Four major groups of cell adhesion molecules have been identified. First, members of the immunoglobulin superfamily (i.e., ICAM-1, ICAM-2, LFA-2), which facilitate cell adhesion by T and B lymphocytes. Second, members of the integrin family (i.e., LFA-1, MAC-1, p-150,95, VLA-1-6), whose function is the dynamic regulation of adhesion and migration. Third, the selectin family (i.e., L-selectin, PADGEM, ELAM-1, LAM-1), which selectively targets leukocyte and neutrophil migration to tissues like lymph nodes or sites of acute inflammation. Last, CD44 which predominantly acts as the hyaluronate receptor, also functions as a general cell adhesion molecule and, additionally, regulates activation thresholds for T cells.[546] Thus, an endotoxin-mediated modulation of CAM can be expected to have crucial effects on leukocyte distribution and function.

When T cells (CD3$^+$ CD16/56-) and NK cells (CD3- CD16/56$^+$) encounter an antigen, mast cells secrete TNF α and IL-1 which in turn induces T- and NK cells to secrete IL-2 and Interferon-γ (IFN-γ).[547,548] IFNγ has been shown to affect the expression of MHC class II molecules by endothelial cells,[549] to increase the binding of T cells to endothelial layers,[550] and to enhance the recirculation of lymphocytes through the lymph nodes.[551] Furthermore it has been shown that IL-1, TNF and endotoxins enhance the binding of lymphocytes and neutrophils to endothelial cell

monolayers.[552,553]

Pyrogenic substances are known to induce leukopenia followed by leukocytosis.[554-559] This recruitment of lymphocytes from and to the blood stream occurs via the postcapillary venules.[560-563] Cell adhesion molecules, expressed on lymphocytes and the endothelial cell layer, mediate rolling, adhesion and subsequent migration of lymphocytes.[561,564-566] This process is regulated by cytokines and is fundamental in understanding the early events following exposure to pyrogenic substances.[567] Leukocyte cell adhesion is mediated by exposure to stimuli such as antigen for lymphocytes or complement factors and leukotriens for monocytes and granulocytes. The forming of cell aggregates or clusters to each other or to other cell types such as vascular endothelial cells appears to be regulated by the activation state of the cell.[568,569]

When inflammatory mediators such as cytokines, thrombin and histamines are released following antigenic exposure (such as endotoxins) they cause the activation of blood vessel endothelium. Cytokines (IL-1, TNF) induce the expression of E-Selectin on endothelial cells after 3-6 hours,[570] whereas thrombin and histamine lead to the release of P-Selectin on endothelial cells within minutes. Additionally, in response to inflammatory cytokines such as IL-1, IL-4, TNF and IFN VCAM-1 and ICAM-1 are induced on vascular endothelium within 6-12 hours and 12-24 hours respectively.[561] Protein kinase C is a mediator of endothelial cell activation by LPS, TNF, and IL-1.[571] The recruitment of lymphocytes into gut-associated tissues of Peyer's patches and nonlymphoid villus regions of the small bowel is also mediated by cell adhesion molecules alpha 4-integrins and beta 2-integrins.[572]

IL-4, for example, a product of activated T cells, can interact with TNF to selectively elevate VCAM-1 expression and the induction of T cell-rich infiltrates.[573] It could be shown that the enterotoxin of *Staphylococcal A* (SEA) increased the cytotoxic T cell response to target cells by binding to major histocompatibility complex (MHC) class II molecules.[574] The cytotoxic activity clearly was mediated by HLA-DR2/ICAM-1 expressed on target cells binding to the integrin heterodimer CD11a/CD18 expressed on effector cells as could be shown by anti-CD11a or anti-CD18 monoclonal antibodies (mAb), but not by anti-CD11b, anti-CD11c, or anti-CD2. Furthermore, it could be shown that resistance of choriocarcinoma cells[575] and melanoma cells[576] to lysis by lymphocytes was partially due to a low expression of ICAM-1 and VCAM-1, respectively. Cell adhesion cell deficient mice exhibited impaired immune responses.[577]

Heat-inactivated gram-negative bacterium *Brucella abortus* not only has been shown to induce the secretion of IL-12 to differentiate Th1 and Th2 cells but also to rapidly increase the expression of the costimulatory molecules B7.1 (CD80), B7.2, and ICAM-1.[578,579] In these studies induction of IL-12 was confirmed by IL-12 p40 mRNA expression and protein secretion by isolated human monocytes. This initiation was blocked by an anti-CD14 monoclonal antibody, suggesting that monocytes bound B. abortus via their LPS receptor. Additionally, NK cell cytotoxicity against K562 target cells was enhanced.[579] Interestingly, LPS induction of B7-1 on human monocytes was superior to IFN-gamma and no response was obtained with isolated IFN-alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-alpha and GM-CSF^{+}TNF-alpha.[576] LPS, rhIL-1, and rhTNF-alpha act via common pathways in endothelial cell activation, a process that is being regulated by protein synthesis.[580]

Increased expression of cell adhesion molecules induced by endotoxins is mediated via elevation of intracellular cAMP concentration ([cAMP]i).[581,582] This activation in turn is sequentially mediated by proteinkinase C in the early phase of activation and by proteinkinase A in the later adhesion of lymphocytes.[583] The adhesion augmented by increased [cAMP]i is due to LFA-1/ICAM-1 interactions between cells because it can be blocked by either anti-CD11a or anti-ICAM-1 mAb. A differential role of protein kinase C (PKC) in cytokine induced lymphocyte-endothelium interaction was established by Eissner et al[584] in vitro. TNF-alpha and LPS-induced ICAM-1 expression on a human endothelium-derived cell line (EA.hy926) was unaffected by the PKC-inhibitor and thus appeared to be independent of PKC activation. In contrast, PKC-inhibitor significantly reduced ICAM-1 expression induced by IFN-gamma and IL-1.

The functional implications of increased CAM expression on lymphocytes and endothelial cells following LPS challenge remain controversial. CAM clearly have been shown to costimulate cytotoxic T cells,[585,586] TIL cells[587,588] and NK cells.[437,589,590] NK cells utilize the beta 2-integrins (CD18/CD1) for firm binding to target cells.[445-447,591] Upon activation, CD11b and CD11c are rapidly increased on human NK cells.[448] Rat Kupffer cells mediated cytotoxicity against a syngeneic hepatoma cell line both by the production of nitric oxide and cell-to-cell adhesion via ICAM-1/CD18.[592] This cytolytic activity of lymphocytes against tumor cells is greatly attenuated when the

lymphocytes are treated with anti- CD11a and anti- CD18.[449] However, peritoneal PMNs derived from patients with bacterial peritonitis have been shown to have increased ICAM-1 levels but were functionally inactive to protect the host from microbial invaders. The authors speculate that an interaction between ICAM-1 and its' counter receptor CD18/CD11a may hinder effector functions. Furthermore, treatment of head and neck SCC cells with recombinant human interferon gamma (rHuIFN), a well known enhancer for the expression of CAM, did increase the ICAM-1/CD11a/CD18 mediated binding of both LAK cells and PBM cells to tumor cells. But on the other hand, cytotoxicity of LAK cells against head and neck SCC cells was reduced after rHuIFN treatment. Additionally, shedding of ICAM-1 from cultured tumors is able to inhibit the CD11a/CD18/ICAM-1 interaction between cytotoxic effector cells and ICAM-1^+ target tumor cells. It is known that shedding of CAM follows activation of resting leukocytes with subsequent upregulation of CAM from intracellular storages.[593,594]

Hershkoviz et al[595] showed that heat-stressed $CD4^+$ T lymphocytes exhibit differential modulations of adhesiveness to extracellular matrix glycoproteins, proliferative responses and TNF-α secretion. Heat-shock treatment of activated $CD4^+$ T cells induced a decrease in the surface expression of beta 1 integrins, which in turn reduced T cell adhesion to fibronectin and laminin. On the other hand the potential of heat-stressed T cells to proliferate and to secrete TNF-alpha was increased.

It should be noted that the expression of cell adhesion molecules not only mediates lymphocyte adherence, migration, extravasation and target cell recognition but also cancer cell metastasis.[596] Analysis of soluble and target cell bound expression of cell adhesion molecules may be an important tool to measure the molecular effects of a given therapeutic intervention. In acute endotoxin overstimulation such as in patients with septic multiple organ failure levels of soluble adhesion molecules (sICAM-1, sELAM-1, sVCAM) were significantly elevated.[597]

Cytokines

Exposure of the host to endo- and exotoxins initiates a complex und multidirectional cytokine cascade. The physiological role of cytokines in our understanding of the cellular and humoral immune mechanisms involved in antitumor activities is a continuously growing body of knowledge and has been extensively reviewed.[567,598-600] Cytokines include the interleukins, the interferons, tumor necrosis factor and the colony-stimulating factors. Clinically, the highest response rates to exogenous cytokine immunotherapy have been seen in malignant melanoma and renal cell cancer.[601] It has been shown that a variety of cytokines are needed for an effective CD8+ T cell mediated cytotoxicity by tumor cell-targeted gene transfer of interleukin 2, interleukin 4, interleukin 7, tumor necrosis factor, and interferon gamma.[602] They have been widely used for immunotherapeutic approaches in cancer treatment (for reviews i.e., refs. 492,603-608).

Recently, different groups attempted to increase the therapeutic potential of these agents with genetic manipulation by introducing genes encoding cytokines into tumour-infiltrating lymphocytes and certain tumor cells.[609] In this chapter some basic mechanisms of LPS induced cytokine secretion and their relevance to immunological responses to cancer shall be briefly summarized. Shieh et al[610] for example, showed that LPS modulated CSF-1, granulocyte-macrophage (GM)-CSF, G-CSF, IL-1, TNF, and Kit Ligand receptors on murine bone marrow cells (BMC) in vivo and in vitro. In vivo, LPS and LPS-induced cytokines (IL-1 and TNF) elicited the secretion of glucocorticoid and CSF activities, which revealed a mechanism for LPS up-modulation of IL-1R on BMC in vivo. Interestingly, application of single cytokines like IFN-gamma could not activate macrophages for tumor cell killing, but required a second stimulus from endotoxin.[611,612]

The cytokines shall be mentioned successively, although this mode of description is certainly not ideal since almost all immunological responses to LPS or other antigens involve a whole cascade of cytokines being induced and secreted.

Not only LPS but also antigens from grampositive organisms evolve powerful immune responses. Two types of cytokine pattern and kinetics have been described after exposure of lymphocytes to (grampositive) *Staphylococcus aureus* enterotoxin A (SEA) and (gramnegative) lipopolysaccharide (LPS).[613] First, LPS stimulation provoked strong production of IL-1 alpha, IL-1 beta, TNF-alpha, IL-6 and IL-8. After LPS exposure IL-1 alpha, IL-1 beta, TNF-alpha and IL-8 were peaking at or before 4 hours after cell stimulation. Also, IL-10 production was evident after 12 hours of cell stimulation. TNF-beta, IL-2, IFN-gamma and IL-4 were not detected in these cultures. All cytokine production, except IL-8, was downregulated at 96 hours. Second, SEA-stimulated cultures showed the highest point in production of IL-1 alpha, IL-1 beta and IL-8 later, after 12 hours. In addition, significant production of TNF-beta, TNF-alpha,

IFN-gamma and IL-2 by T lymphocytes was found with peak production 12-48 hours after initiation of SEA. IL-6 was only discovered in low amounts. Although in the original formula of Coley's Toxin the ratio endotoxin/exotoxin was 7300:1 this observation may in part explain the higher success rate Coley observed after concomitantly administrating endotoxins and exotoxins to his cancer patients.

As mentioned earlier exotoxins, also termed superantigens,[614] are well known inducers of cell adhesion molecules in the inflammatory response[574] and TNF.[615] Recently, superantigens could be shown to complex with the crystal structure of a T cell receptor beta chain.[616] Furthermore, staphylococcal enterotoxin B superantigen conjugated to tumor cells induced strong antitumor activity against Meth A-bearing mice, the antitumor effector cells having been V beta 7- 8- $CD4^+$ T cells.[617] Moreover, even though endotoxin tolerance can be transferred between different bacterial species, it has been shown that the inflammatory response to grampositive and gramnegative infections differs profoundly. Riesenfeld-Orn et al[618] i.e., showed that different cell wall components of grampositive organisms such as pneumococcus exhibited different cytokine induction profiles. Pneumococcal cell surface component did strongly induce IL-1 secretion, being up to 10.000-fold more potent than endotoxin, but did not induce TNF. Table 3 briefly summarizes the effects of the different effector cells and cytokines.

Tolerance

The phenomenon of tolerance to repeated administrations of LPS in human and animals is an important chapter in the history of cancer treatment with bacterial products, since patients have been exposed to repeated vaccinations, often over prolonged periods of time. Beeson[619] and Thomas[620] give early reports on tolerance to bacterial antigens. Subsequent research concentrated on the role of the RES[621,622] and demonstrated that splenectomized rabbits and humans show the same tolerance response as controls.[623] Since splenectomy impairs the production of circulating anti-endotoxin antibodies, it could be concluded that early tolerance up to 72 hours is not antibody mediated. For an early (review see refs. 234,621,624).

More recent studies elucidated the molecular mechanisms of tolerance induction. Lindberg et al[625] showed that tolerance could be induced with a nonpyrogenic, LPS-free O-antigenic polysaccharide hapten, when coupled to an immunogenic carrier protein. Johnson and Greisman[626] established that endotoxin tolerance can be divided temporally in an early and a late phase response. Early tolerance occurs within 24-96 hours following endotoxin exposure and is nonspecific and transient. Late-phase tolerance is mediated by the production of anti-O-specific antibodies, occurs from one week to several weeks following initial endotoxin challenge and lasts for weeks to months. Williams,[627] Madonna and Vogel,[628] and Freudenberg and Galanos[629] established that the early phase tolerance as well as lethality to LPS is a macrophage-mediated phenomenon. Haas et al[630] demonstrated in vitro that monocytic cell lines can be prevented from a TNF response measured by decreased TNF mRNA by preincubating cells with low doses of LPS (10 ng/ml). Interestingly however, preincubation with the same dosage of LPS resulted in increased phagocytosis for the exotoxins of *Staphylococcus aureus*, indicating that some monocyte functions are still active whilst in a state of endotoxin tolerance. Furthermore, repeated administration of endotoxins in murine and human models showed downregulation of TNF-alpha and IL-6, and upregulation of IL-1-beta and G-CSF.[287,631,632] Decrease of TNF-alpha and IL-6 production resulted from an inhibition of gene transcription. Another study found different regulation pathways: Downregulation of TNF-alpha, IL-8, G-CSF, M-CSF and WBC count, and upregulation of IL-6.[286] Other experiments showed that, preexposure of macrophages to very low doses of LPS (≤1 ng/ml) inhibited the expression of TNF-alpha mRNA but not of IL-1 beta mRNA through a noncyclooxygenase-dependent mechanism.[633]

In vitro experiments, however, showed downregulation of the genes for TNF, IL-1 and IL-6 following preexposure of monocytes with low doses of LPS.[634] Also, these authors noted again that the LPS tolerance could be transferred to resistance of a grampositive organism such as *Staphylococcus aureus*, an observation later confirmed by Zhang and Morrison[635] and in contrast to Haas et al[630] and Mathison et al.[636] Interestingly, the amount necessary for inducing a tolerant state is 1.000 time lower than required for the initial induction of TNF production, before tolerance is induced, (picograms vs. nanograms) as pointed out by Mathison et al.[636]

In contrast also, LaRue and McGall[637] demonstrated that endotoxin tolerance is manifested by decreased LPS-induced IL-1-beta transcription. Protection against mucosal injury, nonelevated levels of ileal xanthine oxidase activity and no signs of bacterial translocation in response to repeated administration of LPS was shown by Deitch et al.[638] The same principle could be demonstrated for the administration of TNF-alpha alone. By daily intravenous injections of

recombinant human TNF-alpha (250 ug/kg per diem) healthy rat and mice became resistant to the hemorrhagic effect in the gastrointestinal system. While on the contrary, treatment at 5- or 10-d intervals produced similar results as the initial hemorrhage-causing injection.[639] These results could not be confirmed by Vogel et al,[640] who administered TNF and IL-1 and could not observe a tolerance-like reaction to single application of both cytokines. Combined administration however, induced synergistic toxicity in high doses but could reduce secondary CSF production and reduced the increase of macrophage progenitor cells in lower doses. These results were extended later by Gorgen et al,[641] who showed that pretreatment of mice with recombinant human granulocyte CSF (G-CSF) protected mice against septic shock, a mechanism mediated by reduced LPS-induced serum TNF activity. Interestingly, when tolerant macrophages were incubated with G-CSF in vitro, LPS induced high levels of TNF. These findings implicate that the protective effect of G-CSF is not directly acting on macrophages but acts as a negative feed back signal in vivo. Similar findings were published by Erroi et al,[642] who could not achieve complete endotoxin tolerance by administering IL-6, TNF, or IL-1 alpha in an attempt to mimic LPS-induced tolerance.

Some researchers found additional partial evidence for the molecular mechanisms involved in the phenomenon of endotoxin tolerance at the level of the LPS receptor CD14. Mengozzi et al[643] observed a 50% decrease in the CD14 expression following repeated LPS exposure. Interestingly, cAMP, which is otherwise known to control TNF synthesis, was not affected by preexposure of monocytes to LPS.

Wakabayashi et al[644] demonstrated that pyrogenic tolerance in the rabbit after a single LPS injection is associated with decreased circulating IL-1 beta and TNF levels as well as decreased production of these cytokines in vitro. However, after 7 days pyrogenic hyperresponsiveness to LPS was observed, which was associated with increased synthesis and secretion of IL-1 beta from PBMC in vitro.

As mentioned earlier, pretreatment of cancer patients with IFN-gamma receiving intravenous administration of purified LPS from *Salmonella abortus equi* prevented the downregulation of cytokine secretion, demonstrating that endotoxin tolerance is reversible.[284] In this study, patients pretreated with 50 ug IFN-γ 12 hours prior to endotoxin administration exhibited not only prevention of downregulation of endogenous cytokines (IL-6, IL-8, G-CSF, TNF alpha) normally observed after repeated endotoxin application, but also showed enhanced secretion of these cytokines to levels even higher than those achieved after the first LPS challenge. Therapeutic implications of this fact have been elucidated by Takahashi et al.[645] As already mentioned, the phenomenon of decreased TNF anti-tumor activity resulting from tolerance to repeated applications of exogenous TNF in vivo has been shown to be dependent on the histological tumor type, since this phenomenon has not been observed in all tumors.[643] If tolerance induced decreased anti-tumor activity occurred (i.e., MCA sarcomas, Lewis lung carcinoma), it could be attenuated by addition of IFN-gamma.[643] The same authors further showed that tolerance is a TNF-R55 mediated effect and selectively blocks the TNF-R75-mediated pathway, including IL-1 and glucocorticoid mediated pathways.[646]

As already mentioned, LPS exhibits selective and inverse priming effects on TNF alpha and nitric oxide (NO) production in mouse peritoneal macrophages. Low doses of LPS pretreatment of mouse macrophages increases LPS-dependent IL-6 and TNF alpha production in vitro, and decreases the synthesis of NO by macrophages.[633,647,648] Priming of macrophages with pertussis toxin has exactly opposite effects: increased LPS-induced TNF-alpha production and inhibited LPS-dependent NO production.[649]

Furthermore, glucocorticoids have been shown to play an important role in the phenomenon of tolerance to bacterial products. Adrenalectomized mice do not develop endotoxin tolerance as demonstrated by Evans and Zuckerman[650] and Zuckerman et al.[631] They could show that LPS tolerance involved glucocorticoid-dependent and -independent mechanisms, since corticosterone levels in LPS-treated galactosamine-sensitized and not-adrenalectomized mice were similar to LPS-stimulated normal mice. The glucocorticoid antagonist RU-38486 abolished the development of tolerance induced by TNF[644] and LPS.[651] Furthermore, adrenalectomized mice exhibited an increased sensitivity to IL-1 and TNF.[652] Glucocorticoids are known to suppress the synthesis of inflammatory cytokines,[653,654] and eicosanoids[655] and downregulate inducible nitric oxide synthase.[656]

Although most studies on endotoxin induced tolerance have concentrated on fever and lethality phenomenon, recent evidence suggests that tolerance in response to repeated endotoxin exposure also develops systemically as metabolic,[657] pulmonary,[658] and hemodynamic tolerance.[655]

Translocation

Systemic endo- and exotoxin exposure also leads to increased bacterial translocation from the gut which in turn may compromise the ability of the liver to clear translocated circulating LPS.[659] Bacterial translocation from the gut first to the mesenteric lymph nodes and then to the systemic circulation may play an important role in repeated administration of endo- and exotoxin based vaccines.[19,660,661] The underlying mechanism for this phenomenon is mucosal injury, widening of the intercellular spaces due to tight junction failure below the brush border and capillary leakage.[658,662-664] Disruption of the normal gut flora results in overgrowth with gramnegative, enteric bacilli or aerobe species leading to bacterial translocation. In this respect it is interesting to note, that intraepithelial lymphocytes in the human gut have been shown to possess lytic potential and Th1 and cytotoxic T cell functions, as measured by their cytokine profile.[665] Translocation often has been seen after thermal[666] or mechanical[667] injury, and has been associated with altered host defense capability[519] and multiple organ failure.[668,669]

Tolerance to endotoxin-induced bacterial translocation in response to repeated administration of LPS has been shown by Deitch.[636] This protection against mucosal injury was mediated by nonelevated levels of ileal xanthine oxidase activity, since mucosal injury is known to be mediated by xanthine oxidase-generated production of free oxygen radicals.[660,661]

Most interesting, translocation has been associated with prolonged survival in patients with acute myelogenous leukemia (AML).[133] These authors observed a “paradoxically prolonged survival” in AML patients suffering from a common complication: post-transfusional hepatitis. They alleged the impaired hepatic endotoxin clearance in patients with acute viral hepatitis as the reason for endotoxemia and elevated TNF-α release and also observed virally induced IFN-γ secretion, which in turn acts in synergy with TNF-α anti-proliferative and differentiation inducing.

Hyperthermia

Exogenous induced Hyperthermia as an attempt to mimick the physiological response to fever shall be briefly mentioned (for a review see ref. 670). During the last decades a substantial body of laboratory and animal tumor data has been generated to evaluate the effects of heat on cell survival and growth. Temperature elevation in febrile response has been associated with effects on the recognition, recruitment, and effector phases of the immune response. Temperature elevation appears to affect primarily the phase of recognition and sensitization or activation of mononuclear leukocytes.

Hyperthermia is directly cytotoxic to tumor cells and inhibits repair of radiation damage. These effects are increased by physiological conditions in the tumor bed including acidosis and hypoxia. Tumor blood flow often is reduced in relation to normal tissues, and hyperthermia leads to a further decrease in blood flow depending on temperature and thus augments heat sensitivity by reducing thermal outwash.[671] A pioneer of hyperacidification in combination with hyperthermia has been von Ardenne in Germany.[672-675] He proposed the concept of hyperacidification plus hyperthermia, since hyperthermia is known to induce an acidic microenvironment, a concept later to become known as the cancer multiple-step therapy.[676,677]

Roberts and Steigbigel[247] demonstrated enhanced mitogen response and bactericidal capacity of polymorphonuclear leukocytes following in vitro exposure to febrile like temperatures. A number of in vitro and in vivo studies revealed specific effects of hyperthermia mimicking physiological temperature elevations seen in the febrile response (reviewed in ref. 678). Yonezawa et al[679] observed hyperthermia-induced apoptosis in malignant fibrous histiocytoma cells in vitro. Ensor et al[680] demonstrated a differential secretion of TNF-alpha and IL-6 in vitro in LPS-stimulated human macrophages (HuMoM phi) during 18-h incubation at 40 degrees C. While hyperthermia nearly completely inhibited TNF alpha release, IL-6 secretion remained unchanged. Also a 75-fold increase in the levels of the inducible heat-shock protein 72 (HSP-72) mRNA was observed. Another in vitro study showed increased NK cell cytotoxicity at febrile range (< or = 40 degrees C), but decreased cytotoxicity after exposure of cells to 1 h at 42 degrees C.[681] Niitsu et al[244] reported the synergy of hyperthermia and rTNF on cytotoxicity and artificial metastasis in vitro and in vivo. Whole body hyperthermia increased natural killer cell activity,[682] and cellular immunity in cancer patients,[683] and demonstrated antitumor effects in synergy with exogenous TNF.[684,685]

Synergistic anti-tumor effects of combined hyperthermia and immunotherapies have been documented by a variety of authors. Synergy of local water-bath hyperthermia and TNF alpha in cytotoxicity but also systemic toxicity were found by van der Zee et al.[686] The combination of local but not whole body hyperthermia and immunotherapy with LAK cells and IL-2 in the treatment of multiple pulmonary metastases in mice provided a significant reduction of

pulmonary metastasis from MCA-105 sarcoma cells compared to the control group in a study by Strauch et al.[687] Ex vivo experiments of Kappel et al[688] showed no influence of whole body hyperthermia in subsequent in vitro stimulation of LPS-stimulated mononuclear (BMNC) cells on cytokine production. However, the study suggested that hyperthermia may have altered the sensitivity of BMNC to prostaglandins and in vivo significant cytokine induction was observed for G-CSF, IL-1 beta, IL-6, IL-8, IL-10, and TNF-alpha by Robins et al.[689] Conversely, an earlier study found elevation of IL-1 alpha but not TNF-alpha following whole body hyperthermia.[690]

Heat Shock Proteins

The increased expression of heat shock proteins (HSPs) after hyperthermia treatment or LPS challenge has been shown to correlate with increased immunogenicity of cancer cells through their lysis by alpha/beta T cells.[691] HSPs belong to a group of "stress proteins" secreted after a wide range of stimuli such as oxidative injury, heavy metals, exogenous heat and bacterial toxins. They are classified on the basis of their molecular weight and are divided in five families: low molecular weight family, hsp65, hsp70, hsp90 and hsp100 (for reviews see refs. 586,692,693). HSP have been suggested to act as molecular chaperones in presenting protein structures to the lymphatic system. In this respect they may serve as carriers for antigenic tumor peptides and thereby increase the natural immunity to cancer.[694]

Cancer cells have been reported to have increased expression of HSPs[695] and it is well established that LPS challenge leads to increased expression of HSPs in macrophages,[696,697] blood vessel endothelium[698] and enterocytes.[699] Most interestingly for this review, hsp70 induction has been shown following fever therapy with endotoxins in melanoma patients in vivo and in vitro.[700] However, this study revealed hsp70 induction in vivo only in 50% of the cases exposed to a Coley Toxin like preparation (Vaccineurin), while in vitro 100% of peripheral blood mononuclear cells could be shown to express hsp70 following endo- and exotoxin challenge, indicating additional mechanisms for control of expression in vivo.

Increasing evidence suggests that HSPs could confer protection against oxidative injury, noxious molecules, and bacterial toxins.[701-703] In stressed cells HSPs 72 appears to be essential for survival during and after exposure to cellular injury. HSPs furthermore have been suggested to present cancer antigens to the human immune system, especially $CD8^+$ T lymphocytes[704] and have been suggested as potent cancer vaccines.[705] Moreover, it has been shown that exogenous cell components which normally are only presented in association with MHC class I proteins, can be directed into the endogenous pathway, conferred by MHC class I molecules, and also recognized by CTL.[706] Furthermore, it was shown that LPS induced a HSP 60 mediated increase in expression of ICAM-1 on blood vessel endothelial cells.[698] This finding bears important implications for the attraction of leukocytes following the use of bacterial vaccines.

HSP gene transcription increases during or direct after heating; a correlation between the synthesis of HSP and thermotolerance has been found in normal and malignant cells.[707] HSPs appear after the activation of a so-called heat-shock transcription factor. This protein has been isolated and purified by Zimarino and Wu,[708] and Wiederrecht et al.[709] Nuclease digestion studies have clearly demonstrated that, until the cell is stressed, the protein does not bind to the appropriate promoter region of the gene. Upon activation, the factor binds to the heat-shock element and gene activation results. It is assumed that ubitiquin is involved in the activation process. It has further been suggested that the signal for the induction of the heat shock response relates to the cell's reaction to the presence of abnormal proteins. Yet, a common way of gene activation is not known. Most organisms use transcription as the primary control, and translation control for "fine tuning" for individual HSP synthesis.[710] Signals involved in HSP synthesis use the second messenger cascades which possibly is triggered by an intra-membrane protein aggregation. However, it is not known which steps lead to the activation of the transcription factor. Structure of genes and promoter regions and the transcription factor are known.

Interestingly, it has been shown that prior induction of HSPs protect the organism from subsequent LPS induced hypotension by inhibition of the overproduction of nitric oxide via reduced iNOS mRNA induction[711-713] and endothelial cells from apoptosis in vitro via hsp70 and inhibition of LPS-mediated O2–generation.[714,715] However, while prior induction of HSPs exerted a posttranslational control of TNF alpha release in LPS-stimulated alveolar macrophages,[716,717] concomitant application of TNF alpha enhanced LPS-induced heat shock protein production in vivo.[696] Moreover, the myocardium has been shown to be protected from endotoxin induced ischemia by prior induction of HSPs.[718] Additionally, macrophages exposed repeatedly to LPS and IFN-gamma have been shown to

become resistant to the deleterious effects of nitric oxide by expressing hsp70.[697] It also should be noted that HSPs contribute to the development of drug resistance against chemotherapeutic against in cancer therapy and therefore extreme hyperthermia should not be applied immediately before chemotherapy.[719]

From the preceding remarks on hyperthermia and HSPs it is tempting to speculate, that in the treatment of cancer patients with hyperthermia and bacterial vaccines it may be meaningful to expose patients first to hyperthermia and secondly to an endotoxin/exotoxin challenge. As it has been shown by Hotchkiss et al,[720] the protective effects of hyperthermia beginning 1 to 2 hours after heat exposure and reach a maximum at 12 hours. In this way patients would raise their core temperature first by induction of whole body hyperthermia and be prevented from experiencing unpleasant shivering and muscle cramps often following administration of fever induction. Additionally, it may be speculated that the protective effects of hyperthermia, i.e., induction of HSPs may aid in preventing the often intense side effects like hypotension and endothelial cell damage.

Alpha$_2$ Macroglobulin

Endotoxins and exotoxins have been shown to affect alpha$_2$-macroglobulin (alpha$_2$M) with their proteolytic enzymes.[721] Although it has been shown that streptokinase suppresses some immune functions such as chemotactic activity,[722] or trypsin the IL-2 mediated proliferation of T cells,[723] these enzymes may have interesting qualities on regulating the cytokine metabolism by activating alpha$_2$M as shall be discussed further. The hypothesis is postulated that enzyme-activated alpha$_2$M downregulates overexpressed cytokines and lymphocyte reactions in vivo, but may stimulate normal and desired immune responses. In this respect it has to be noted that most immunosuppressive actions of activated alpha$_2$M and the respective enzymes have been reported in in vitro systems for T lymphocyte proliferation without[724,725] and with[726] IL-2. Streptokinase has been shown to have inhibitory effects on in vitro tumoricidal activity of human serum,[433] and in vivo it has been demonstrated to be a powerful inhibitor of tumor growth.[423]

Alpha$_2$M is the regulator of distribution and activity of many cytokines including TNF alpha,[727] TGF-beta 1,[728-731] TGF-beta 2,[724-726] platelet derived growth factor (PDGF),[732,733] IL-1 beta[734,735] and IL-6[736] (reviewed in refs. 737,738). Importantly, the alpha$_2$M-bound cytokines and alpha$_2$M-bound proteolytic enzymes both keep their biological activity.[739]

Alpha$_2$M is a high molecular weight (Mr_{human} =718,000) major plasma proteinase inhibitor and reacts with a broad diversity of endopeptidases.[740] The enzymes are getting “trapped” in a well defined region of the alpha$_2$M molecule, which then undergoes dramatic conformational changes, while the enzymes keep their proteolytic function.[741] An enzyme carrying form of alpha$_2$M is called the activated or “fast” form of alpha$_2$M.[742,743] The fast form of alpha$_2$M preferentially binds TNF alpha, TGF-beta 1 and -beta 2, and IL-1 beta while PDGF, NGF and IL-6 bind to the native or “slow” form.[744] Importantly, the fast form of alpha$_2$M becomes activated for increased receptor-mediated endocytosis by exposing a latent alpha$_2$M receptor-recognition domain to hepatocytes,[745] macrophages,[746-748] and fibroblasts.[749,750] The cytokine carrying alpha$_2$M then undergoes rapid clearance by binding to hepatic-, macrophagic-, and fibroblastic-alpha$_2$M-receptors.[751-753] It is further suggested that alpha$_2$M plays an important role in cytokine testing bioassays, which may has been underestimated.[754]

However, in vitro exposure of macrophages to LPS and IFN gamma, but not to TNF, TGF beta-1or IL-6 induced a significant downregulation of the alpha$_2$M-receptor/low density lipoprotein receptor.[755] These studies need to be confirmed in vivo, but allow the hypothesis that the downregulation of the alpha$_2$M-receptor/low density lipoprotein receptor may act as an inhibitory feedback mechanism for the binding of proteolytic enzymes.

Toxicity

Toxicity of endo- and exotoxin-based cancer therapies can be considerable. The administration of such therapies therefore only should be performed by qualified medical providers and should include immediate access to conventional emergency support. Self-administration of salmonella endotoxin has been reported resulting in shock and multiple-organ dysfunction.[756] In the experienced hand however, the administration of this therapeutic approach does not impose a greater risk to the patient than conventional procedures such as chemotherapy. Informed consent may help to increase compliance and reframe the understanding of the patient in respect to beneficial effects of “fever-therapy”. Additionally, psychoneuroimmunology research has shown that compliance with and possibly efficacy of

therapy can be increased if the patient is fully informed. Even more, numerous authors report induction of fever and immunopotentiation with endotoxin without any toxic reactions (reviewed in refs. 106,757,758).

Endo- and exotoxin mediated toxicities can include hypotension, hepatotoxicity, induction of herpes labialis, muscle spasms and cramps, and in severe cases shock and circulatory failure (cardiovascular effects reviewed in ref. 759). These side effects always should be noted and classified according to WHO criteria.[760] High doses of endotoxin result in systemic effects such as circulatory failure and death.[761] A number of treatments have been suggested to diminish the dose limiting toxicities. In attempts to limit exogenous TNF toxicities Brouckaert et al[762] suggested “methylene blue, an inhibitor of the nitric oxide (NO)-induced activation of the cytosolic guanylate cyclase, without the indispensable protective properties of NO being affected” to prevent hypotension. Furthermore, they suggested anti CD11a to prevent IL-12 mediated sensitization to TNF and alpha 1-acid-glycoprotein and alpha 1-antitrypsin to protect against TNF-induced hepatotoxicity by reducing the release of platelet-activating factor.[763] LPS mediated toxicity and what is more lethality however, can not be explained by TNF induction alone.[176]

Further toxicity is mediated by IL-1 as has been shown by the successful blocking of lethal LPS challenge with a recombinant receptor antagonist protein to IL-1.[764] The same authors demonstrated manganous superoxide dismutase induced protection against lethal LPS challenge but not against LPS-mediated toxicities with a 24-hour pretreatment of a single dose of TNF.[765] Recombinant IL-1 receptor antagonist also protected against TNF-induced lethality.[766] Moreover, IL-1 alpha has been demonstrated to mediate the microcirculatory changes in the intestinal mucosa observed after systemic endotoxin exposure, including increased adhesiveness of leukocytes and mucosal damage.[767]

Recently, the vascular pathophysiology of endo- and exotoxin induced hypotension and extravasation has been described as being the result of activation of the bradykinin-Hageman-factor-kallikrein cascade.[768] Inhibitors of kinin and kallikrein have been suggested subsequently to block the shock induced by bacterial proteases by blocking the kallikrein-kinin cascade. Another study explained bacterial-associated vasculitis by IL-1 alpha mediated secretion of IL-6 and IL-8.[769]

Possible effects of endotoxin induced lung injury have been shown at the level of alveolar macrophages for enhanced secretion of IL-1, TNF-alpha, and prostaglandin E2.[770] Finally, it is of interest to note that nontoxic polysaccharide derivatives free of lipid A have been shown equally effective in enhancing humoral immunity in FLV immunocompromised animals, both in vivo and in vitro.[33,771,772] The nontoxic polysaccharide derivative however, did not induce TNF, and cells needed to be stimulated with IL-2 prior to LPS exposure to produce IFN.[272] On the other hand the same authors reported effective inhibition of Meth A sarcoma with the use nontoxic LPS derivatives low in endotoxin.[773]

There are numerous substances, which efficiently counteract the toxicities of endotoxin- and exotoxin-based immunotherapies but it is important to keep the possible interactions with immunological effects in mind, which these preparations might elicit additionally and thus interfere with the efficacy of the treatment approach. The classical antipyretics include prostaglandin synthesis inhibitors indomethacin, ibuprofen and glucocorticosteroids next to antipyretics such as aspirin and paracetamol. Endogenous glucocorticoids play an important role in protecting the host against TNF mediated LPS sensitization.[774] Additionally, chlorpromazine has been shown to protect against endotoxic shock by inhibiting peripheral and brain TNF, and upregulating IL-10 production.[775] Furthermore, the cytokine inhibitor pentoxifylline has been suggested as an antipyretic by lowering TNF and IL-6 levels.[776]

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Figures

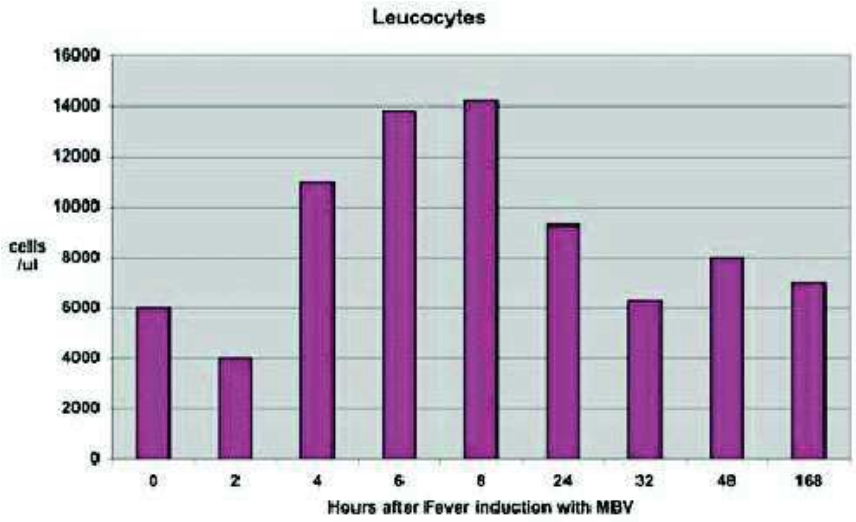

Figure 1

Time dependent exemplary induction of IL-1 in a patient after induction of fever up to 39.8°C with a biological pyrogen (Vaccineurin).

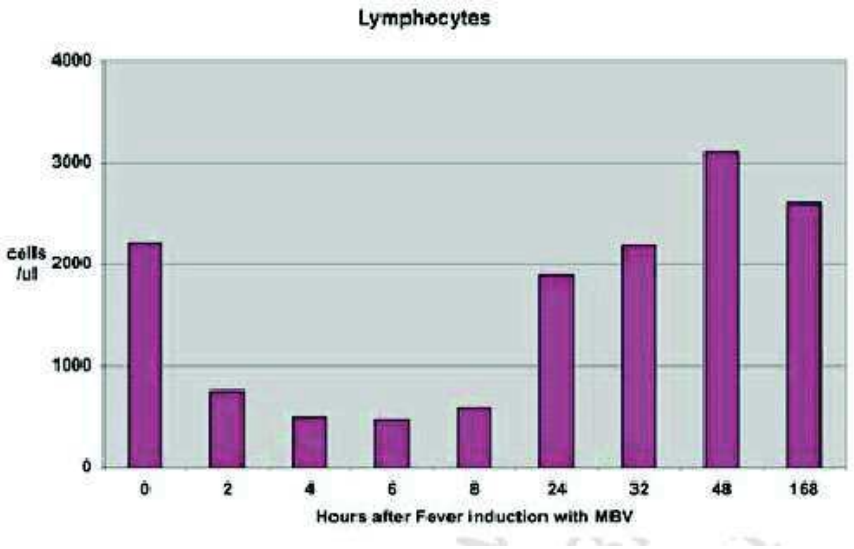

Figure 2

Emigration, homing, proliferation and activation of leukocytes in a patient after induction of fever up to 39.8°C with a biological pyrogen (Vaccineurin) depending on time.

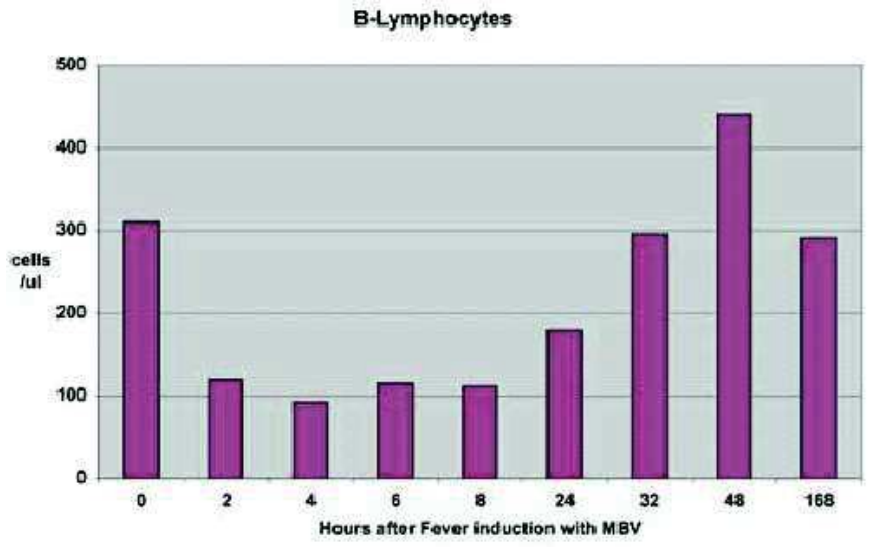

Figure 3

Emigration, homing, proliferation and activation of total lymphocytes in a patient after induction of fever up to 39.8°C with a biological pyrogen (Vaccineurin) depending on time.

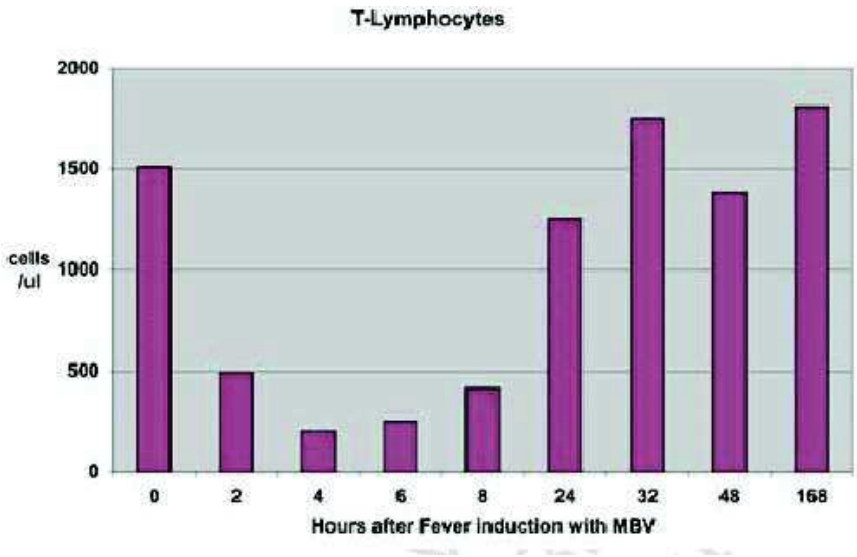

Figure 4

Emigration, homing, proliferation and activation of B-lymphocytes in a patient after induction of fever up to 39.8°C with a biological pyrogen (Vaccineurin) depending on time.

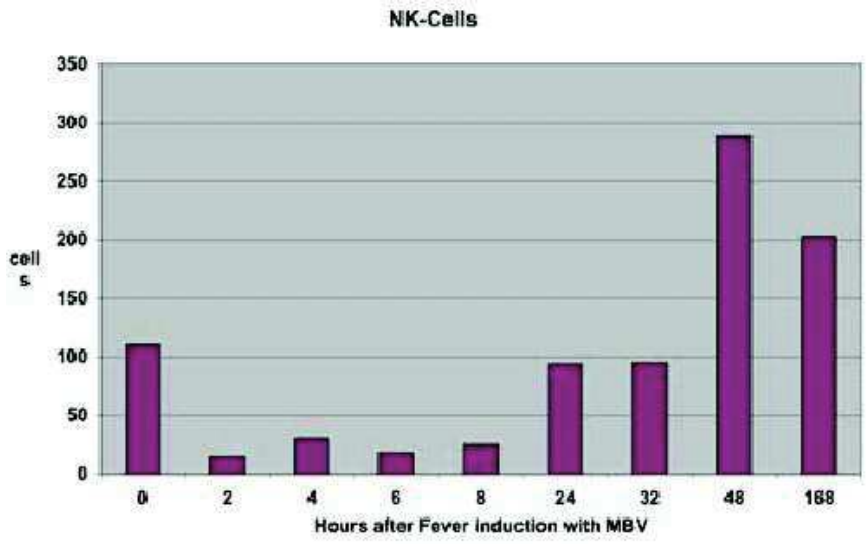

Figure 5

Emigration, homing, proliferation and activation of T-lymphocytes in a patient after induction of fever up to 39.8°C with a biological pyrogen (Vaccineurin) depending on time.

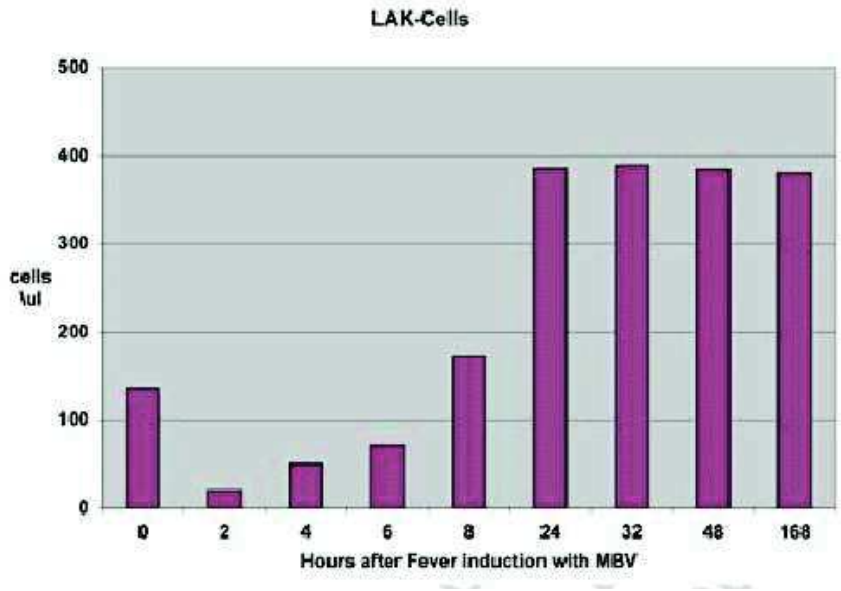

Figure 6

Emigration, homing, proliferation and activation of NK-cells in a patient after induction of fever up to 39.8°C with a biological pyrogen (Vaccineurin) depending on time.

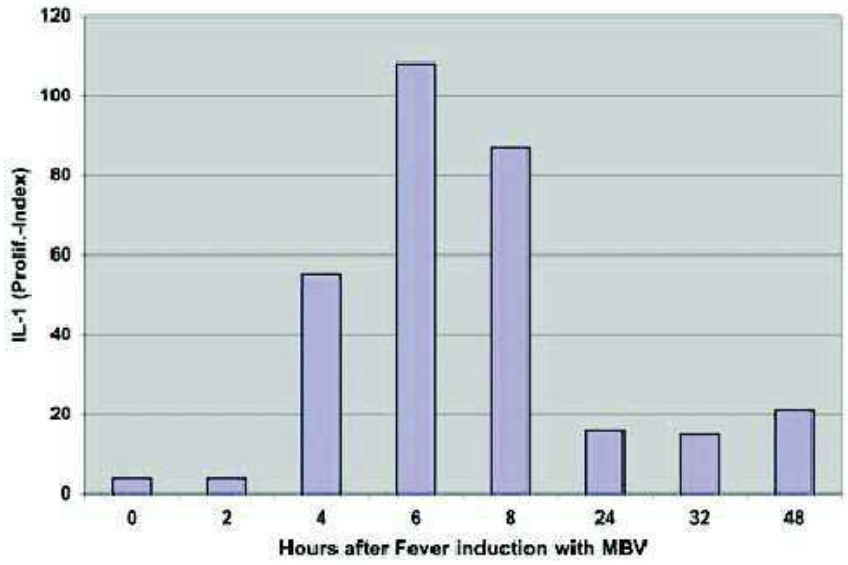

Figure 7

Emigration, homing, proliferation and activation of LAK-cells in a patient after induction of fever up to 39.8°C with a biological pyrogen (Vaccineurin) depending on time.

Tables

Table 1 Spontaneous remission listed under tumor types

Types	References
Bone Tumors	Levin,[135] Cole,[136] Callan et al,[137] Copeland,[138] Eisenbud et al,[139] Collignon et al[140]
Brain Tumors	Margolis and West,[141] Kapp,[130] Rao et al[142]
Burkitts Lymphoma	Bluming and Ziegler[143]
Colorectal Cancer	Nowacki and Szymendera,[131] Fucini et al[132]
Gastric Cancer	Rebollo et al,[144] Zambrana et al[145]
Gynecological	Friedrich Jr[146]
Head and Neck Cancer	Temesrekasi,[147] Woods[148]
Hepatocellular Cancer	Chien et al,[149] Grossmann et al,[150] Markovic et al,[151] Tarazov[152]
Leukemia	Hart,[153] Dock,[123] Dreyfus,[154] Bassen et al,[155] Pelner et al,[124] Paolino and Sartoris,[156] Vladimirskaia,[157] Hardisty,[158] Burgess and de Gruchy,[159] Wyszkowski et al,[160] Matzker and Steinberg,[129] Wiernik,[161] Barton et al,[162] Conrad and Barton,[163] Foon et al,[164] Vinogradova and Ivanina,[165] Sanz and Sanz,[166] Zhu and Quian,[167] Kizaki et al,[125] Maekawa et al,[168] Treon and Broitman,[133] Frick and Frick,[169] Delmer et al,[170] Musto et al,[171] Jono et al,[172] Lefrere et al[173]
Lung Cancer	Takita,[127] Ruckdeschel et al,[128] Greentree,[174] Marcos Sureda et al,[175] Sanchez et al,[176] Mentzner[177]
Lymphoma and	Zygiert,[178] Bluming and Ziegler,[143] Ziegler,[179] Gattiker et al,[180]
Non Hodgkin Lymphoma	McClain et al,[181] Kempin et al,[182,183] Grem,[184] Drobyski and Qazi,[185] Wolf,[186] Sureda et al,[187] De Berker et al,[188] Sawada et al,[189] Heinzlef et al[190]
Suggested Mechanisms	Wolfenheim,[115] Tsubura et al,[191] Bagshawe et al,[192] Muckle et al,[193] Schwartz et al,[194] Cho-Chung and Gullino,[195-197] Remy et al,[198] Berendt,[199,200] Pedersen et al,[201] Bolande,[202] Nowotny,[111] Baker,[203] Stone,[204] Jarpe et al,[205] Seachrist,[206] Halliday et al[207]
Melanoma	Gunale and Tucker,[208] Wormald and Harper,[209] Wagner et al,[210] Cook,[211] Grafton,[212] Haliday et al,[207] Motofei,[213] Maurer and Kolmel[134]
Multiple Myeloma	London[214]
Prostrate Cancer	Schurmans et al[215]
Renal Cell Cancer	Katz and Schapira,[216] Mangiapan et al,[217] Edwards et al[218]
Retinoblastoma	Hunter,[219] Verhoeff,[220] Jain and Singh[221]
Reviews	Bruns,[112] Eschweiler,[113] Rohdenburg,[114] Dobson and Dickey,[222] Everson,[116-119] Huth,[126] Stephenson et al,[120] Cole,[121,122] Sindelar,[223] Nauts,[101] Challis and Stam,[224] Seacrist,[206] Kaiser[225]
Sarcoma	Watson,[226] Shore,[227] Penner,[228] Berner and Laub,[229] Nauts and Fowler,[103] Weintraub,[230] Mizuno et al,[231] Lei et al[232]

Table 2 Mechanisms following stimulation of humoral and cellular defense

Type I	*Living cultures of Streptococcus erysipelatis* (1891).
Type II	*Erysipelas toxins* contained heat-inactivated (100°C) erysipelas toxins (1892).
Type II	*Erysipelas toxins* sterilized by passage through a Kitasato filter and not subjected to heat sterilization (1892).
Type IV	*Mixed filtered toxins* were the first mixed filtered toxins. Always freshly prepared, not-heated filtrate containing the soluble toxic products of Streptococcus pyogenes and Serratia marcescens (1892-1894).
Type V	*(Buxton's) Mixed filtered toxin*. Buxton grew Streptococcus pyogenes and Serratia marcescens together in the same broth and filtered through a Kitasato filter (1894).
Type VI	*(Buxton's) Mixed unfiltered toxin* followed the procedure in type V but instead of being filtered they were heated for one hour at 50°C - 60°C (1894-1907).
Type VII	*Coley's mixed serum* contained serum from Streptococcus pyogenes and Serratia marcescens prepared in the same way as diphtheria antitoxin (1894).
Type VIII	*Mixed toxins, filtered and unfiltered*. Prepared by Lister Institute in London these toxins were similar to type IV, V and VI (1894-1943).
Type IX	*Mixed unfiltered toxins* prepared by Parke Davis & Co were the first commercially available preparations of Streptococcus pyogenes and Serratia marcescens (1899-1906).
Type X	*Mixed unfiltered toxins* of Streptococcus pyogenes and Serratia marcescens prepared by Dr. Martha Tracy (1906-1907). ("The two organisms were grown separately and heated to 75°C for one hour {15°C higher than Type VI}. The amount of prodigiosus {serratia marcescens} was 5 mg per cc of the mixed toxins, determined by Kjeldahl's method of nitrogen determination. After mixing and bottling the toxins were again sterilized for two hours at 75°C. These were the most powerful of all, according to Coley.[11] They proved to be too toxic, due to large amounts of bacillus prodrigiosus"; cit. after Nauts[105]) (1906-1907).
Type XI	*(Tracy) Mixed, unfiltered toxins* of Streptococcus pyogenes and Serratia marcescens were prepared like Type X, with a lesser amount of Serratia marcescens. ("This product appears to have been used in the largest number of successful results (Nauts et al[104]); cit. after Nauts[105]) (1907-1922).
Type XII	*(Tracy) Mixed filtered toxins*. Similar to type XI but filtered.
Type XII F	*(Parke Davis) filtrate*. Similar to type XII but stated to have been weaker (1906-1915).
Type XIII	*(Parke Davis) Mixed, unfiltered toxins* were similar to type XII but Nauts assumed that…"although this product was more potent than type XII, it is now known that the active toxins and enzymes of streptococci are more thermolabile than those of bacillus prodigiosus, and therefore it would appear that heating the organism for 2 1/2 hours must have destroyed much of the streptococcus toxins"; (cit. after Nauts[105]). (1915-1951).
Type IX	*(Sloan-Kettering) Mixed, unfiltered toxins* prepared after Tracy XI formula with new strains of from Streptococcus pyogenes and Serratia marcescens (1946-1953).

Table 3 Mechanisms following stimulation of humoral and cellular defense

Effector Cell	Cytotoxic Effect	Secondary Cellular Activation	Cytokin-Activated Cell
Macrophage	Direct cell-mediated	TNF alpha	Macrophage
NK cell	Surface-TNF		(LAK cell)
LAK cell	Perforines	IFN gamma	Macrophage
Granulocyte	Cytokin-mediated		(LAK cell)
Mast cell	TNF alpha	IL-1	T- cell
Mast cell	LT (TNF beta)		(LAK cell)
Mast cell	IL-1	IL-2	LAK cell, NK- cell
Mast cell	IFN- gamma		
Mast cell	LR	IL-4	LAK cell
Mast cell	NKCF	LR	NK- cell
Mast cell		CSFs	bone marrow

Abbreviations: CSFs = colony stimulating factor; IFN gamma = interferon gamma; IL = interleukin; LAK = lymphokine-activated killer cell; LR = leukoregulin; LT = lymphotoxin; NK = natural killer cell; NKCF = natural killer cell cytotoxic factor; TIL = tumor-infiltrating lymphocyte; TNF = tumor necrosis factor.

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