CHAPTER 2

THE PSYCHOIMMUNOLOGICAL INTERACTION

The previous chapter summarised some of the past and present views of the mind-body dilemma and presented an introduction to the psychoneuroimmunological approach. This and the following chapters will deal with the psychoneuroimmunological interaction as an extension of the stress paradigm. The present chapter demonstrates the psychoimmunological link and, although most pathways probably involve the two main stress axes, the main focus will be on the psychological and immunological aspects, rather than on the underlying neurohormonal pathways. Eperimentally-derived evidence for the psychoimmunological interaction is shown in psychological conditioning of the immune response, the placebo response, the effects of psychological stress, the effects of psychological stress on the immune function during infectious conditions and in several other phenomena. Also dealt with is the bidirectional influence between the immune system and disorders, as well as related behavioural characteristics, of the DSM-1V classification. In conclusion, the implications of the psychoimmunological interaction during *in utero* and neonatal life are briefly discussed. The link between this chapter and the rest of the thesis is maintained by, when appropriate, referring to the role of the two main stress axes and psychological influences such as perception and coping. However, a detailed discussing of such aspects is deliberately avoided, partially to demarcate the boundaries of the chapter and partially because they are treated more extensively in later chapters. The chapter is summarised in a diagram, demonstrating the pervasiveness of the interaction.

Introduction

Evidence for the interaction between the psycho- and the immunological components of psychoimmunology can be found in phenomena such as conditioning, the stress

response, in conditions such as infections and tumour development, autoimmune diseases, therapeutic interventions, biofeedback mechanisms, the placebo effect and many others. Immunological involvement in certain behavioural phenomena, in a number of neurological diseases and in psychiatric disorders give further substance to the existence of a mutual influence between psychological functions and immunology. Examples of such phenomena will be provided in support of the assumption of a pervasive psychoimmunological interaction.

The contents of the chapter are summarised in Figure 2.1 (p2.3). The legend to Figure 2.1, and the description below the legend, are given on the subsequent page.

The following examples of psychoimmunological interactions are discussed:

2.1 Immunological effects of conditioning as an example of the psychological influence on the immune system

2.2 The placebo effect as an example of the psychological influence on the immune system.

2.3 The influence of stress on the immune system as an example of the psychological influence on the immune system.

2.4 Other interesting associations between the immune system and behaviour

2.5 Mental disorders and behavioural traits as examples of the psychoimmunological interaction.

2.6 Early life experiences and psychoimmunology

2.7 The psychoimmunological interaction and cerebral laterality

2.8 The psychoimmunological interaction in overview

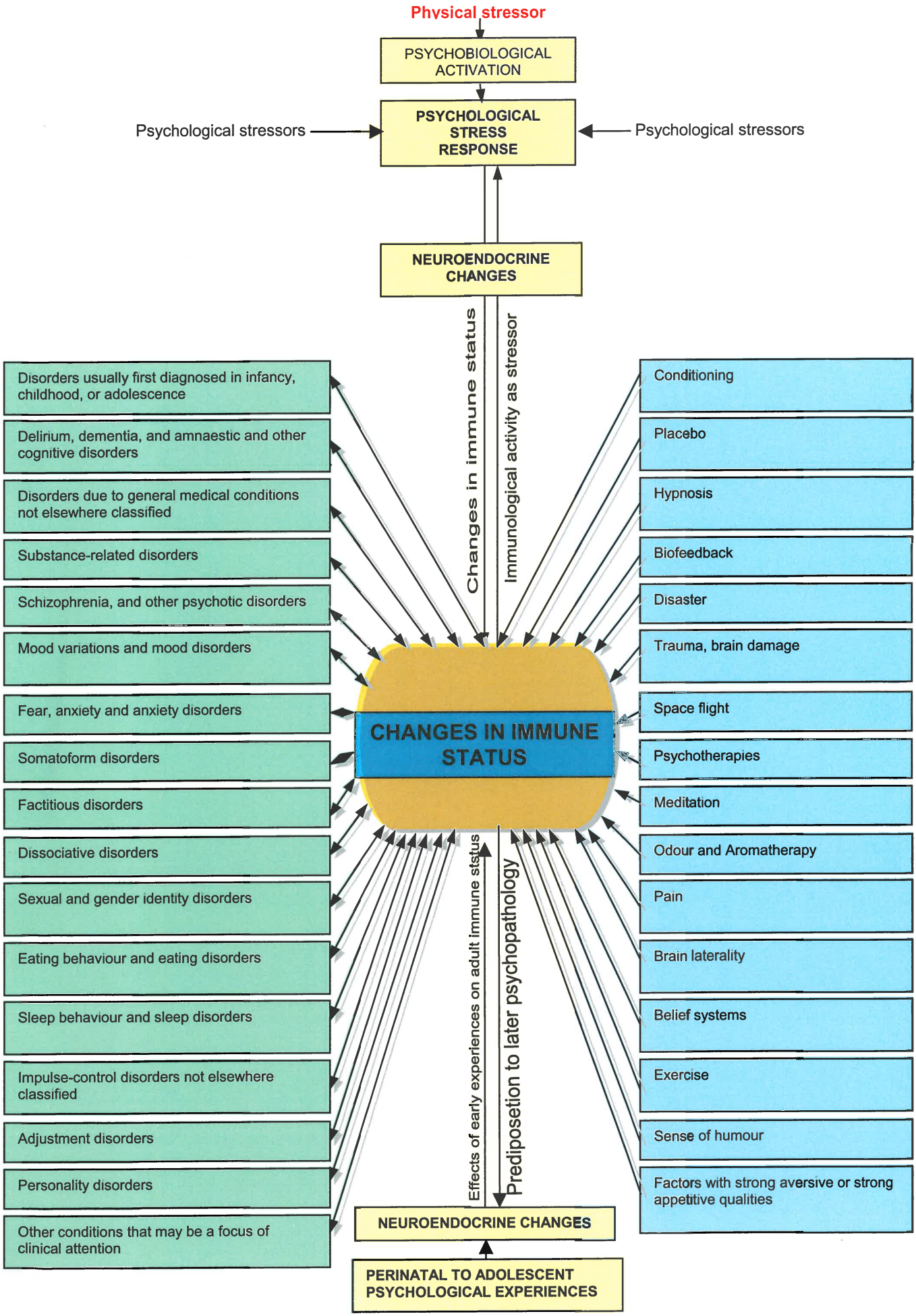

Figure 2.1: Conditions and behaviours with proven alterations in immune status

Legend to Figure 2.1.

Figure 2.1: Conditions and behaviours with proven alterations in immune status.

[Figure 2.1 shows that any form of psychological stressor, of enough significance to elicit the psychological stress response, can lead to immune alterations (middle-top of diagram). Physical stressors that cause psychobiological activation will also initiate the psychological stress response with subsequent immunological effects (middle-top of diagram). Other conditions and factors reported to be associated with alterations in immune responsivity are depicted on the right of the diagram. On the left side of Figure 2.1 mental disorders and associated behaviours, known to have some kind of immunological involvement, are presented. Right at the bottom-middle of the diagram is shown that early life experiences can influence both the psychological and immunological status. These are mediated through stress-induced neuroendocrine changes and may last for life, predisposing the individual to behavioural and immunological disturbances in adulthood.] See references under discussions of the immunological involvement in these phenomena

2.1 Immunological effects of conditioning as an example of the psychological influence on the immune system

Solid proof for the interaction is derived from classical conditioning where the perception of the characteristics of a conditioned stimulus elicits a response in accordance with the perceived stimulus rather than with the actual stimulus. The concept of this type of conditioning is historically ascribed to Ivan Pavlov after his classical experimental work in which salivation could be instigated by means of a conditioned response (1). However, conditioned manipulation of the immune response is generally known since 1920 (2,3). The first recorded psychological-induced immune provocation in humans would appear to be the induction of *rose cold* by means of an artificial rose (4). It is, however, conceivable that this type of immunological exploitation could have been practised, premeditated or not, throughout the existence of mankind. Examples of immunological manipulation through psychological conditioning will be shown from both animal experimentation and human observation.

2.1.1 Conditioning in animals

The following couple of paragraphs will deal with the psychoimmunology of conditioning in animals. The link between the stress axes and conditioning is discussed in later chapters as part of the psychoneurological interaction .

Numerous reports were published since the initial immuno-conditioning experiments of Metalnikof and Chlorine in 1920 (2,3). Early experimental work on immunoconditioning include the conditioning of natural killer cell activity, examination of the time span between stimulus-pairing and re-exposure, the psychological induction of asthma in guinea-pigs and prolongation of graft survival through associative conditioning. Descriptions of much of this earlier experiments can be read in the first edition of *Psychoneuroimmunology,* 1981 (5).

A major part of animal experimental conditioning involves immunopharmacological work performed by pairing an immunomodulating drug (unconditioned stimulus, UCS) with some immunological-neutral, but usually psychological-aversive or novel factor (conditioned stimulus). A technique often used is the so-called conditioned taste aversion (CTA) paradigm. It is, however, not possible to talk about immune conditioning without mentioning the names of Ader and Cohen, 1991 (6) who, since the 1970's, provided us with a bank of evidence on the immunological effects of immune conditioning. Examples of experimental modulation of the immune system through conditioning, where immune responses were shown to be evoked or inhibited by immunological inert substances, can be seen in Table 2.1, as adapted from the review by Ader and Cohen (6). The reader is referred to the article for references to the original authors. The examples seen in Table 2.1 are representative of numerous publications that confirmed that immunological activity can be altered by conditioning.

Table 2.1: Examples of modulation of the immune response in rodents through the process of conditioning.

Unconditioned Stimulus	Conditioned Stimulus	Immunological Measure	Unconditioned response	Conditioned response
Cyclophosphamide (=immuno-suppresive drug)	Saccharin	Ab (SRBC)	Decreased response	Decreased response
	Sucrose	Ab (SRBC)	Decreased response	Decreased response
	HCl	Ab (SRBC)	Decreased response	Decreased response
	Saccharin/ environment	Ab (SRBC)	Decreased response	No conditioned response
	Saccharin	PFC (SRBC)	Decreased response	Decreased response
		PFC (TNP-SRBC)	Decreased response	Decreased response
		IgM	Decreased response	Decreased response
		PFC (TNP-LPS)	Decreased response	Decreased response
		AB (*Brucella abortus)*	Decreased response	No conditional response
		Pneumococcal polysaccharide	Decreased response	No conditional response
		GvH Response	Decreased response	Decreased response
		DTH response	Decreased response	No conditioned response
		DTH response	Increased response	Increased response
		Lymphocyte proliferation	Decreased response	Decreased response
		NK cell activity	Decreased response	Decreased response
	Saccharin/LiCl	NK cell activity	Decreased response	Decreased response
	Saccharin/vanilla	Total white blood cells	Decreased response	Decreased response
		Arthritic inflammation	Decreased response	Decreased response
	Saccharin	Lupus Plasmacytoma	Decreased response	Decreased response
Methotrexate	Saccharin	Ab (SRBC)	Decreased response	Decreased response
Levamisole	Saccharin	T-helper : suppressor ratio	Increased response	Increased response
Antilymphocyte serum	Saccharin	Mixed lymphocyte reaction	Decreased response	Decreased response
Allogeneic cells	Environment	CTLp	Increased response	Increased response
Bovine serum albumin	Odours	Histamine	Increased response	Increased response
Egg albumin	Environment	Mast cell protease II	Increased response	Increased response
Poly I:C	Saccharin/LiCl	NK cell activity	Increased response	Increased response
	Odours	NK cell activity	Increased response	Increased response
LiCl	Saccharin	AB (SRBC)	No unconditioned response	No conditioned response
		DTH Response	No unconditioned response	Decreased response
Rotation				
Acute/CY	Environment	Ab (SRBC)	Decreased response	Decreased response
Chronic/CY	Environment	Ab (SRBC)	Increased response	Increased response
Electric shock	Environment	PFC (SRBC)	Decreased response	Decreased response
	Environment	Lymphocyte proliferation	Decreased response	Decreased response
	Environment	Lymphocyte proliferation	Decreased response	Decreased response

Adapted from a review by Ader and Cohen (6); SRBC = sheep red blood cells; Ab (SRBC) = anti-SRBC serum antibody; GvH = graft versus host; DTH = delayed type hypersensitivity; PFC =plaque forming cells ; TNP = Trinitrophenyl ; NK cell = natural killer cell.

Table 2.1 shows some changes that occur in a number of immunological parameters as a result of conditioning. The practical implications of immune modulation through conditioning can, however, perhaps be better understood from the following experimental evidence that involve immunological status rather than individual immunological parameters.

- Classical conditioning in rats has been shown to alter the course of experimentally induced autoimmune diseases such as systemic lupus erythematosis and adjuvant arthritis – a disease very similar to rheumatoid arthritis in man. Results from several laboratories showed that by pairing an immunosuppressive substance (UCS) with an immunological inert factor (CS), mortality can subsequently be delayed by administration of the inert substance alone (7).
- Experiments in rats indicate that heart allograft survival can be prolonged by behavioural conditioning. It was repeatedly shown that immunologically neutral, but psychologically aversive or novel substances (CS) can, after pairing with an immunosuppressive drug, exert immunosuppressive effects similar to that of the drug (UCS). It is obvious that the modulating pathways must involve the higher brain function centres, and it is highly likely that the peripheral conditioned immunological response is expressed via, at least partially, the two main stress axes. In fact, published evidence does indeed show such involvement (8).
- One of the best known behaviourally conditioned immune responses is the modulation of body temperature, i.e., the modulation of thermoregulation. Most of the work on this aspect of conditioning is based on the taste aversion paradigm. It is by now known that the effects of most pyretic, as well as anti-pyretic drugs can, after conditioning, be mimicked by administration of the conditioned stimulus alone (9). A spin-off from experiments on conditioned thermoregulation is derived from what was originally seen as controversial results. A number of workers initially tried to employ lithium chloride as the conditioned stimulus – this due to the aversive properties.

However, results from these and other laboratories showed LiCl not only to be an antipyretic substance in its own right, but also to have immuno-augmentative functions. The immune enhancing properties of LiCl would appear to be most pronounced in immunocompromised conditions (10).

- An interesting finding is the restoration of immune function through olfactory stimulation by means of various fragrances (11,12). It is suggested that abolition of the stress-induced immune suppression could result from the limbic system-olfactory bulb neural connections in that an inhibitory influence from the olfactory bulb would block the stress activation of the limbic system. Although considered an example of immune conditioning (12), this experimental work does not strictly conform to the classical conditioning paradigm. It is, however, included as it does indeed demonstrate the influence of the neurological aspects on the immune system and could perhaps contribute to our understanding of the effect the aromatic fragrances are said to have on stress-induced immune suppression.

It is important to note that certain phenomena are repeatedly observed in conditioning experiments with animals (6,8), and that there are strong indications that at least some results could be extrapolated to humans. Included are the following facts

- Extinction of the conditioned immune response can, as with other types of conditioning, occur. The extinction of the conditioned immune response occurs along the well accepted lines described in most relevant psychology text books.
- There is no direct relationship between the magnitude of the conditioned alterations in behaviour and that in immune function.
- Conditioned changes in immunity may be completely dissociated from changes in behaviour.
- Conditioning may contribute to the immunopharmacological tolerance that develops with repeated exposure to certain immunomodulatory drugs.

Theoretical extrapolation of the results on the immunological conditioning in animals to the clinical situation is starting to point towards a number of possible applications that could be beneficial in the treatment of patients. An example of this can be found in the

conditioned pharmacological effects in conditions where it is clinically desirable to reduce the dosage of drug administration to an autoimmune patient or transplant recipient (13). It is envisaged that pairing of the conditioned response to a low drug dosage may, as indicated by animal research, suffice to deliver the required immune response without the deleterious effects of high drug dosages. The opposite effect, i.e., that of pharmacological tolerance is unfortunately also a possibility.

2.1.2 Conditioning in man

Published examples of conditioned immune alteration in humans do exist, but one can with a fair amount of certainty say that this type of conditioning forms part of the child-rearing style of virtually every family where the attitudes of parents to disease conditions influence the immunological status and the proneness to disease in their children, and even in themselves. It is also feasible to expect that the media and perhaps more so television and other electronic information systems can condition the public to the extent that the immune system could be affected. One could even surmise that a large number of the psychological therapies for immune-related disorders are based on conditioning.

Below are given some cases as examples of experimentally induced conditioned immunomodulation in humans.

- The induction of allergic rhinitis by conditioning has experimentally been shown (14). The unconditioned stimulus was, in this case, an allergen paired to allergen-free physiological saline as conditioned stimulus. The results of the study point toward a role for conditioning, expectation and the placebo effect in the management of allergic disorders.
- Immunopharmacological tolerance has been described as a conditioned response (8). In a Pavlovian conditioning model of tolerance the administration procedure is considered to be the conditioned stimulus and the central affects of the drug as the unconditioned stimulus. It is suggested that repeated pairing of the administration procedure to the drug effect may lead to the development of a conditioned response in anticipation of the drug effects which may either lead to attenuation of the response, or to compensatory opposition to the effect, i.e., immunopharmacological tolerance. Indications are that

context specific tolerance can be reduced by conditioning procedures such as extinction, latent inhibition and partial reinforcement. As for other conditioned immunological manipulations, a central position in the mechanistic pathway is ascribed to the antigen processing cell and cytokines.

- A well known experiment is the one where individuals were painted with a methylene blue solution (CS) containing the extract from a Japanese lacquer tree (UCS) – a substance known to cause eczema. After a number of CS-UCS pairings the skin response could be induced with the methylene blue only (15).

There seems to be some inconsistency in the results of conditioning experiments in humans. These will not be discussed here, but it is important to note that the ability to condition human subjects is dependent on the personality of the experimenter, as well as on that of the volunteer. Research on the conditioned immunological response in man as, well as in animals are starting to pay dividends in terms of finding the underlying physiological mechanisms. Although the picture is as yet not completely clear, dependence on the degree of psychobiological arousal, as well as on the involvement of the major stress-associated neuroendocrinological systems are becoming evident (7,16). It is also more than speculative to expect that the psychological influence on immunity may involve the limbic system, and that the final pathway of the conditioning influence on the immune system may find expression largely through the two axes discussed in subsequent chapters. The mechanisms involved would appear to be very similar to that proposed for the placebo effect, which is referred to in the following subdivision.

From the examples of the psychoimmunological interaction in terms of conditioning presented here, and from other literature, it would appear that modulation of the immune system through both strictly Pavlovian and taste aversion conditioning can lead to

- Suppression of immunoreactivity, i.e., conditioned immunosuppression
- Enhancement of immunoreactivity, i.e., conditioned immunoenhancement
- Stimulation of mechanisms which compensate for the unconditioned immunological response, i.e., conditioned compensatory responses

The question should be asked whether conditioning of the immune response has any biological or practical significance. It does indeed appear feasible that psychological conditioning of the immune response could be used to the benefit of patients in a) to reduce the amount of a drug required in the treatment of chronic diseases, b) to optimize the efficacy of a given treatment, c) to decrease the susceptibility to naturally occurring diseases (16), and perhaps d) to reduce the symptoms of chronic inflammatory diseases.

2.2 The placebo effect as an example of the psychological influence on the immune system.

Placebo is defined as a harmless treatment thought to have no measurable effect on the condition to which it is applied. The mere fact that the term *placebo response* exists indicates that an effect is indeed expected upon administration of the placebo. Although the term *placebo effect* or response is generally used it would be more correct to use the term placebo response for positive or beneficial outcomes and the term nocebo response for negative or harmful outcomes. Theoretically a placebo may be anything from a sugar coated pill to the influence of the physician. Evidence is available to show that the immune system can be altered by placebo administration. Scientifically the positive placebo effect on the immune system is ascribed to the alleviation of stress axis activation. We have recently published an article on the placebo response (17). Rather than describing examples from this article it will be attached to the thesis. However, it is perhaps necessary to deal with some information. To quote from the article:

> *It is generally assumed that psychological aspects play an important role in the placebo effect. Benson and Friedman proposed three components required to manifest the placebo effect*
>
> *Positive expectation on the patient's part*
> *Positive expectation on the doctor's part*
> *A good doctor-patient relationship*
>
> *Several psychological theories are offered as explanation for the placebo effect, including*
>
> *The anxiety theory*
> *This theory pertinently refers to a diminished stress axis activity as a factor in the placebo response. The theory states that the mere act of getting help or taking*

control reduces the negative affective component associated with the symptom. Hereby the whole sympathetic tonus is said to be reduced. (The role of sympathetic tonus in immune function is discussed in a later chapter, suffice to say that excessive sympathetic tonus could cause or exacerbate a variety of immune conditions and that a direct link exists between anxiety and the sympathetic system.) This effect is more lasting in patients with state anxiety than in patients with trait anxiety.

The cognitive theory
Here the emphasis is on expectation. Higher cortical centres involved in cognition, can override subconscious emotional responses. The expectation determines the cognitive readjustment of appropriate behaviour. This is said to explain the different effects of different verbal instructions. Any process that increases a patients expectation of improvement is likely to relieve stress and will reduce cortisol levels and sympathetic activation that may adversely influence health problems. The emphasis remains on the individuals perception, colouring a neutral stimulus with positive or negative expectation. As in the case of the anxiety theory, the stress axes are again implicated.

[Ker and Viljoen, 2000 (17)]

2.3 The influence of stress on the immune system as an example of the psychological influence on the immune system.

The previous paragraphs dealt with the immunological effects of psychological conditioning and with the placebo response. It was seen that the majority of experimental work on conditioning involves aversive stimulus conditions. There is thus, but for the repetitive factor, a very thin line separating a large part of the conditioning experiments from the stress experiments. This is an important factor as it is becoming ever more evident that the effects of conditioning are eminently dependent on the way the animal perceives the stimulus, and that factors such as conditionability traits and preparedness (16) are major determinants of outcome. Another possible similarity between the conditioning and stress experiments can be found in the stress-induced changes in the presence of infectious diseases where a pairing of two different stressors is found. The one stressor being the physical-psychological stressor and the other the disease-inducing organism.

For the purpose of this discussion stress will be seen as the non-specific stress response, as opposed to the compensatory mechanisms (specific stress responses) which occur as negative feedback mechanisms in response to specific stressors like cold, hypoglycaemia,

hypotension, hypoxaemia and other specific disturbances. It should, however, be remembered that specific stressors, can give rise to the non-specific stress response if the negative feedback mechanism for the specific homeostatic disturbance cannot cope, or if the stressor leads to psychobiological arousal. In the majority of animal stress experiments, and in a smaller number of human stress experiments, the psychological or non-specific stress response is indeed evoked by the application of specific stressors which, due to their aversive or novel characteristics, are able to induce psychobiological arousal.

The deleterious effects of psychological stress on the general well being and especially on resistance to the development of infectious disorders have been known for decades, if not for longer. What is perhaps surprising is the fact that the magnitude of the potential impact of psychological stress has, until recently, been overlooked and often even slighted by the medical and veterinarian professions and that psychologists tend to focus on the psychosocial consequences rather than on the organism as an integrated mind-body unit. The present writing will focus on the psychoimmunology of stress, without consideration of the neurological mechanisms involved. The humoral and cellular immune changes will also, but for a few exceptions, not be dealt with. However, the two major neurological stress pathways and their effects on the immune system, i.e., the neuroimmunological aspects, are discussed in chapters 4, 5 and 6 and the psychoneurological interactions of these pathways in chapters 3 and 5. Many other neurohormonal mechanisms are, however, also known to have an influence on the immune system - some boosting the system, and others suppressing it (18). Of interest is the fact that the majority of them also have behavioural effects and that the individuals psychological disposition usually has an influence on the activity of all such substances. A discussion of their mechanisms of action and functions is beyond the scope of this writing.

The following paragraphs will thus deal with the psychoimmunological interaction during stress, firstly in animals and thereafter in man. Some examples of the type of immunological alterations will be provided in table format. Thereafter, in concordance

with the interdisciplinary nature of the work, no further attempt will be made to provide any in depth coverage of the underlying immunological mechanisms.

2.3.1 Psychological stress and immune function in animals

Clear evidence for the psychoimmunological interaction in animals can be found in the psychological-induced immune alterations seen under conditions of stress. Intuitive knowledge existed about the relationship between stress and immune suppression long before the formal recognition of immunology as an independent scientific field. It is, however, only over the last couple of decades that the effect of stress on immunological parameters could be quantified. In animals the largest part of evidence for the interaction is derived from laboratory experiments where various kinds of stressors were applied and a variety of immunological factors assessed. It is at this stage necessary to note that in many of the animal experiments the psychological state, i.e., the emotional stress, is generally elicited through the application of physical stressors under the premise that the stress response is stressor-intensity, rather than stressor-modality specific. The stress condition thus becomes a state of altered psychological homeostasis with the physiological response expressed as immunological alterations at least partially mediated through the central noradrenergic/sympathoadrenomedullary (CNA/SAM) and central corticotrophin-releasing hormone/hypothalamo-pituitary adrenal (CRH/HPA) systems. Similar psychoimmunological interactions are seen in the stress-alteration of the immune response to infection and in the development of tumours in the presence of psychological stress.

One of the first documented associations between stress and infectious pathology in animals was the observation by Pasteur that cold water immersion stress lowered the resistance of chickens to the anthrax bacillus (19). The finding would, however, not appear to have stimulated significant further research into this kind of association. Renewed scientific interest in the effect of stress on the immune system was again seen only around the 1930's with the work of Selye (20). It should be remembered that the original work by Hans Selye, which led to, what Selye termed the general adaptation syndrome, as well as to the description of the stress triad, was derived from results of animal experimentation (20). The work of Selye would seem to have given some impetus

to this area of research. It was, however, only during the 1980's that a widespread scientific interest in the psychoimmunological interaction started to develop. One of the major reasons was the fact that immunology had now become a recognised scientific field and that new immunological techniques were rapidly being developed. Various new disciplines started to emerge such as neuroimmunomodulation, psychoneuroimmunology, neuroendocrinoimmunology and others – generally not much more than synonyms for variations on the neuroimmunological/psychoimmunological interaction. It should be acknowledged that these disciplines are all extensions on the erstwhile stress paradigm. The psychoimmunological interaction has, however, lately become acknowledged to stretch far beyond the condition of stress.

Proof of the interaction between the immune system and the psychological disposition in animals, as witnessed under conditions of stress, is provided on the following couple of pages. Examples of experimental results on the effects of stress on the immune system, the effect of stress on the immunological defense against infections, as well as the effect of stress on the development of tumour growth in animals can be seen in Table 2.2.

Table 2.2: Examples of psychological stress-induced modulation of the immune response in animals.

Psychological Stressor	Additional Variable	Experimental Animal	Effect on Immune system	Reference
Sound stress	**Exposure time** **Acute stress** **Intermediate duration** **Chronic (20-39 days)** **Longer than 39 days**	**Mouse** **Mouse** **Mouse** **Mouse**	**Suppression of lymphocyte proliferation** **No change from baseline** **Increased lymphocyte proliferation** **Return to baseline values**	**Monjan & Collector, 1977 (21)**
Surgical stress	Stress intensity **Extreme** **moderate**	**Rat** **Rat**	**↓ cytostatic activity of lung macrophages** **No effect on cytostatic activity of lung macrophages**	**Toge *et al*, 1981 (22)**
Shuttle box stress with footshock	Age **12-18 Months old** **25 months old**	**Male Fisher rat** **Male Fisher rat**	**↓ splenic lymphocyte responsity to ConA** **no effect on responsivity to ConA**	**Odio *et al*, 1987 (23)**
Mild to moderate footshock/tail shock	Controllability **unpredictable/uncontrollable** **controllable**	**Sprague Dawley rat** **Sprague Dawley rat**	**↓ lymphocyte response to ConA and PHA** **0 to ↑ lymphocyte response to con A and PHA**	**Laudenslager et al 1983 (24)**
Inescapable/ escapable shock	Controllability **inescapable shock** **escapable shock**	**Fischer rat** **Fischer rat**	**↓ splenic natural killer cell (NKC) activity** **no efect on NKC activity**	**Shavit et al 1983 (25)**
Social Interaction				
Premature maternal separation and isolation	Gender: **Male** **Female**	**Wistar rat** **Wistar rat**	**↓ lymphocyte response to PHA suppression less significant than in male rats** **negative correlation between degree of submissivenes and immunisation**	**Ackermam et a;. 1988 (26)**
Maternal deprivation	Age of separation before weaning	**Mouse**	**separation before weaning: ↓ humoral immune responses in later life**	**Michant et al, 1981 (27)**
Enforced submissiveness	Rank order (**dominance – submissiveness**)	**Rat**	**negative correlation between degree of submissiveness and immunisation-induced antibody production** **↓primary antibody response to SRBC in losers**	**Fleschner et al 1989 (28)**
Dyadic interaction	**Defeat**	**Mouse/rat**	**↑↑B -lymphocytes; ↓T- lymphocytes ↑↑ T-helper cells; ↓ suppressor/cytotoxic cells;**	**Bohus et al, 1989 (29)**
Chronic social stress of colony aggregation	**Stress quality dominant**	**Male rats**	**↑↑ T-helper: T suppressor ratio; ↓ cytotoxic T-cell response; ↓Iℓ-2 sensitivity, T Iℓ-2 production; ↑↑ConA proliferation; ↑↑PHA proliferation**	**Bohus et al, 1989 (29)**

Psychological stressor	Additional variable	Experimental animal	Effect on immune system	Reference
	subdominant	**Male rats**	**↓↓total lymphocyte; ↑B lymphocytes ↓T lymphocytes; ↑ T helpercells; ↓ T-suppressor /cytotoxic cells; ↑T helper: T suppressor ratio; ↑cytotoxic T-cell response; ↑ Iℓ-2 sensitivityIℓ-2 production; ↑ ConA and PHA proliferation**	**Bohus et al, 1989 (29)**
	subordinate	**Male rats**	**↑total lymphocytes; ↓ B lymphocytes; ↑T lymphocytes; ↓T helper cells; ↑ suppressor/cytotoxic cells; ↓↓ helper suppressor ratio; ↓ cytotoxic T cell response; ↓ Iℓ-2 sensitivity; ↓ Iℓ-2 production ↓ ConA and PHA proliferation**	**Bohus et al 1989 (29)**
	Outcast	**Male rats**	**↑T suppressor/cytotoxic cells ↓↓T-helper: T suppressor ratio; ↑ cytotoxic T cell response; ↓Iℓ-2 sensitivity; no change in Iℓ-2 production; ↓ConA and PHA proliferation**	**Bohus et al, 1989**
Housing condition and inoculation of Moloney sarcoma virus	Behavioural characteristics **fighting**	**Female mice**	**Smaller tumour development**	**Amkraut and Solomon, 1972 (30)**
	nonfighting	**Female mice**	**Larger tumours**	
The effect on tumour growth				
Shaking stress and Melanoma tumour	Behavioural characteristics **social activity/passivity**	**Female hamsters**	**Social passivity suppresses tumour growth**	**Temoshok et al 1987 (31)**
Social stress and cancer	Living conditions **. isolation**	**Female hamsters**	**↑ development of mammary tumors ↑ malignant mesanchymal tumors ↑ spontaneous leukemia**	**Bohus and Koolhaas, 1991 (reviewed) (32)**
	. sex-segregation		**↑ growth of murine sarcoma virus**	
	. crowding as opposed to paired housing		**↑ death from mesenchymal cancers**	
	. social disorder (removal of young)	**Mice**	**↑ appearance of mammary tumours**	
	. behaviour of significant others	**Mice**	**behaviour of co-housed animals have favourable or unfavourable effects on tumour-bearing animals**	

Psychological Stressor	Infectious disease caused by	Experimental Animal	Effect on Immune system	Reference
Effect on infectious disease vulnerability				
Crowding	***Salmonella typhimurium***	**Mouse**	**↓ antibody response, ↑ susceptibility**	**Edwards and Dean, 1977 (33)**
Forced exercise	***Pasteurella haemolytica***	**Calf**	**↓ pulmonary phagocytes, = severity**	**Binkhorst et al, 1990 (34)**
Forced exercise	***Pasteurella haemolytica***	**Calf**	**↓ pulmonary phagocytes, ↑ severity**	**Anderson et al, 1991 (35)**
Social stress (low degree)	***Escherichia coli***	**Chicken**	**↓ susceptibility**	**Gross, 1984 (36)**
Social stress (high degree)	***Escheria coli***	**Chicken**	**↑ susceptibility**	**Gross, 1984 (36)**
Forced swimming	***Francisella tularensis***	**Mouse**	**= mortality**	**Ilbäck et al, 1984 (37)**
	Influenza A virus		**↑ mortality**	
Transportation (short)	***Pasteurella haemolytica***	**Calf**	**↑ mortality**	**Cole et al, 1988 (38)**
Transportation (long)			**↓ mortality**	
Restraint	***Mycobacterium avium***	**Mouse (f)**	**= antimycobacterial activity of macrophages, = mycobacterial growth**	**Brown and Zwilling, 1993 (39)**
		Mouse (m)	**↓ antimycobacterial activity of macrophages, ↑ mycobacterial growth**	
Constant illumination or heat	***Escherichia coli***	**Female mouse**	**↑↑ uroepithelial shedding ↑↑ PMN mobilization, ↓ rate of infection**	**Dalal et al, 1994 (40)**
		Male mouse	**↑ uroepithelial shedding ↑ PMN mobilization, = rate of infection**	
Sound	***Vesicular stomatitis***	**Mouse**	**↓ IFN production = neutralizing antibody ↑ mortality, encephalitis**	**Chang and Rasmussen, 1965 (41)**
Avoidance learning	***Poliovirus***	**Mouse**	**↑ mortality, paralysis**	**Johnsson and Rasmussen, 1965 (42)**
Isolation	***Encephalomyocarditis***	**CD-1 mouse**	**↑↑ mortality**	**Friedman et al, 1970 (43)**
		BALB/c mouse	**↑ mortality**	
Forced swimming	***Coxsackie virus B3***	**Mouse**	**↑ mortality, myocarditis**	**Gatmaitan et al, 1970 (44)**

Psychological Stresstor	Additional Variable	Experimental Animal	Effect on Immune system	Reference
Forced exercise	***Coxsackievirus B3***	**Muse**	**↓ neutralizing antibody**	**Reyes and Lerner, 1976 (45)**
Heat	***Newcastle disease***	**Chicken**	**↓ / ↑ antibody response**	**Beard and Mitchell, 1987 (46)**
Immobilization	***Influenza A***	**Mouse**	**↓ IFN-α production, ↑ mortality**	**Ben-Nathan et al, 1989 (47)**
Restraint	***HSV-1***	**Mouse**	**↓ lymphadenopathy, ↓ HSV-specific CTL activity, ↓ NK activity,**	**Bonneau et al, 1991 (48)**
Restraint	***HSV-1***	**Mouse**	**↓ migration of HSV-specific CTLm, ↓ activation of HSV-specific CTLm**	**Bonneau et al, 1991 (48)**
Isolation	***SIV***	**Monkey**	**↓ lymphocytes, ↓ leukocytes, ↓ survival**	**Capitanio and Lerche, 1991 (50)**
Restraint	***Influenza A***	**Mouse**	**Delayed seroconversion, = magnitude of antibody response, =Ig class composition**	**Feng et al, 1991 (51)**
Restraint	***Influenza A***	**Mouse**	**↓ virus-specific IL-2 production, = antibody response, ↓ pulmonary lesions**	**Sheridan et al, 1991 (52)**
Restraint	***HSV-1***	**Mouse**	**↓ lymphadenopathy, ↓ HSV-specific CTL production**	**Bonneau et al, 1991 (53)**
Restraint	***Influenza A/PR8***	**DBA/2 Mouse**	**↑↑ corticosterone, ↓ antibody ↓ lymphadenopathy, ↓ mortality, ↓ pulmonary inflammation**	**Hermann et al, 1993 (54)**
Restraint	***Influenza A/PR8***	**C57BL/6 Mouse**	**↑corticosterone, ↓ antibody ↓ lymphadenopathy, = mortality, ↓ pulmonary inflammation**	**Hermann et al, 1993 (54)**
Restraint	***Influenza A/PR8***	**C3H/HeN Mouse**	**↓ lymphadenopathy, ↓ antibody, ≅ kinetics of GC response to infection, = mortality, ↓ pulmonary inflammation**	**Hermann et al, 1993 (54)**
Restraint	***Influenza A/PR8***	**DBA/2 Mouse**	**↓ lymphadenopathy, ↓ antibody, ≅ kinetics of GC response to infection, ↓ mortality,**	**Hermann et al, 1994 (55)**
Restraint	***Influenza A/PR8***	**C57BL/6**	**↓ lymphadenopathy, ↓ antibody ≠ kinetics of GC response to infection, = mortality**	**Hermann et al, 1994 (55)**
Exposure to a predator	***Hymenolepis nana***	**Mouse**	**↓↓ lymphoid tissue, ↑↑ reinfection**	**Hamilton, 1973 (56)**

Psychological Stressor	Additional Variable	Experimental Animal	Effect on Immune system	Reference
Handling	***Hymenolepis nana***	**Mouse**	**↓ lymphoid tissue, ↑ reinfection**	**Hamilton, et al 1973 (56)**
Cold, heat	***Toxoplasma gondii***	**Rat**	**↑ pulmonary disease**	**El-Fakahany et al, 1988 (57)**

The examples of stress-induced changes in the immunological activity of animals, as seen in Table 2.2, clearly show that severe stress will generally have an immune suppressive effect and thus can predispose the animal to infections and tumour growth.

As can be seen in Table 2.2, various kinds of stressors can be employed in order to cause psychological stress in animals. Many of them are in fact physical stressors and it is assumed that their application will - and it has indeed neurohormonally been proved - lead to psychobiological arousal. As such it can with a fair amount of certainty be said that the process will involve psychologically-induced activation of the two main stress axes. The degree of psychological arousal is, however, not always easy to assess in animals.

Psychological stress can, as was previously mentioned, be evoked by the application of either physical or psychosocial stressors. Physical stressors generally employed to provoke psychological stress in animals include restraint, cold exposure, electrical shock, surgical trauma, noise, vibration, forced swimming, constant illumination, transportation and other stressor models. In the restraint models, immune suppression is generally evidenced by a decrease in almost all aspects of the immune response and in the containment of autoimmune diseases. In the various electrical shock models, the general conclusions are that of immune suppression. Significant deviations do, however, occur and should not summarily be ignored.

Many factors which contribute to variations in the immunological outcome can be traced back to psychological phenomena and include factors such as the perception of controllability, whether the shock is escapable or not, the degree of predictability, and in general the coping response (58,59). Previous exposure to inescapable shock can further give rise to a conditioned stress response upon re-exposure to stress-related cues. Obvious implications with regard to repeated punishment and, punishment-associated cues, on the immune status can be derived from this fact.

As in the case of the physical stress model, various forms of the social stress model also exist, including the social group models, different forms of dyadic interaction, as well as the social isolation and high population density models (59 and Table 2.2). In the social group model of dominance versus sub-dominance or outcasts, a superior immunocompetence is generally seen in the dominant animal. The immunological outcome in dyadic interactions depends very much on perception and coping style. In the resident-intruder paradigm of the dyadic model, social defeat would generally be reflected in immunosuppression, while variable outcomes are reported in the aggressive-*versus*-nonaggressive version of the dyadic social stress model. Results on the latter experiments would seem to indicate a different immunological outcome in males and females (59). It would be interesting to know whether this difference can be ascribed solely to inherent neurohormonal difference or whether social training with regard to gender role is present in rodents. In the social isolation model the results depend on various factors, including the customary social structure of the experimental species. The majority of research, according to the isolation stress model, focus on early maternal deprivation or early weaning which, in general, would appear to be detrimental to normal immunological development. This could perhaps be seen as support for the mother-infant bonding as opposed to the mother's milk nutritional value concept for immunocompetence. Interesting neurohormonal support for the positive immunological effect of maternal stimulation comes from work on rat pups where maternal stimulation in infancy was shown to result in lower levels of ACTH, corticosterone, and CRH mRNA, and higher levels of the immune stimulating-related growth hormone mRNA (60). Although not speculated on by the author, it could very well be seen as the opposite of stress presensitisation and, if extrapolated to humans, it could be surmised that a

favourable mother-infant bond would afford the infant a degree of protection against the development of stress-induced psychological and possibly immunological disturbances in later life. The central role of CRH in the central stress response and in hyperresponsivity is discussed in Chapter 5. Results from a number of studies support the possibility that unfavourable mother-infant relationships can have negative effects on the immunological status and that such effects could last into adult life (58,61,62,63,64,65,66). Peer separation in the young has similarly been shown to induce an immunosuppressive influence (58,65). Of interest is the fact that a return to normal immunological responsivity has been observed upon reuniting of the separated young, and that, at least in the case of the mother-infant separation, the immunosuppressive effect could be prevented by keeping the infant in familiar surroundings (58). Various factors in the environment could possibly contribute to pacify the young, among others familiar odours. This possibility is supported by immune enhancing experimental results from animals exposed to olfactory cues of social origin and from immune suppressive results of animals exposed to odours derived from stressed animals (58). The effect of in utero stress is discussed later in this chapter under early life experiences and psychoimmunology.

In the high population density version of the social stress model, stress-induced immunosuppression is generally associated with an increase in population density. High population density is further seen to have a negative influence on the survival rate of animals with infection or with cancer. In most of the social stress models individual preference in social activity seems to be an important explanatory variable (58). Nevertheless, whether active or passive, the emotional stability of the animal appears to be a major factor. Assessment of emotional stability can, however, be rather problematic in animals.

Factors like emotional reactivity and personality, although difficult to assess in animals, have been reported to influence the immunological effect of stressors. In certain animal strains a link is known to exist between the emotional reactivity to conflict and the immunological reactivity to stress (67). It is likely that this strain-dependent co-variation between immunological and behavioural traits can be linked to neurohormonal

differences in response to stressors. Such strain-dependent, stress-induced neurohormonal differences have indeed been reported (68,69). Similar neurohormonal-dependent variablity in the immunological effects of stress is sure to be expressed as a result of personality traits. A type C coping style has even been suggested to be associated with cancer onset and progression (70). Scientific evidence is also available to neurohormonally linked coping style with the type of immune response. High activation of the CNA/SAM-axis has been recorded in males where a more aggressive coping style was observed, while CRH/HPA-axis activation would appear to predominate in males with a more passive coping style (71,72). The immunologial implication of this difference in neurohormonal response is self-evident from the immune responses to be described in chapters 4 and 5.

The degree of controllability over the environment, the predictability of the stressor application and the coping style of the animal appear to have a major impact on the immunological outcome – irrespective of the stress model applied. In the previous paragraph reference was made to the neurohormonal differences noted between aggressive and non-aggressive male mice and rats. Similar neurohormonal differences exist between active and passive stress avoidance animals and in animals with different levels of social activity. The active coping styles of aggressive males versus the more passive coping style of the non-aggressive males, the characteristic of active stress avoidance *versus* passive stress avoidance, as well as differences in social activity would all seem to contribute to the variability in the immune responsiveness to stress (59,67,71,72,73). The more active coping styles where the animal takes control of the situation would generally appear to predict a more favourable immunological outcome.

The importance of the sense of control which an animal experiences under conditions of stress is further supported by a recent review dealing with the influence of mental state on somatic health in animals (74). Some important research findings reviewed include the immunological effects of stress-induced emotional states such as

- Fear and anxiety which were shown to lower immunocompetence against cancer and infectious disease to the extent that it could increase the mortality rate. Interesting

examples include fear or anxiety provoked by expectation of punishment or aversive treatment.

- The emotions associated with disruptions of social bonding or affiliations where placement in familiar surroundings or the presence of familiar peers seemed to lessen the immunosuppressive effect of disruption in social bonding and affiliation.
- Boredom caused by insufficient mental stimulation or socially deprived environments which is reported to lead to immunosuppression.
- The cognitive-emotional state of learned helplessness, a condition known to be characterised by the perception of no control over the environment. As in several other recent publications, the fundamental importance of a sense of control for the immune response against the development of tumour growth, infectious diseases and other immune-related disorders are discussed and the negative influence of helplessness and unpredictability of events once again stressed.
- A feeling of control, in general, which is said to be the ultimate discriminating factor between immunosupression and immune-enhancement in the face of stress.

A large part of our knowledge on the effects of stress on the immune system is derived from animal experimentation. Various problems do, however exist in the interpretation and integration of results from different laboratories (58,59,75,76). Research in the field of psychoimmunology has now reached a stage where it should be possible to solve some of the research problems and inconsistencies of results by proper planning of experimental design. A major problem with the comparative assessment of the influence of stress on both immunological competence and containment is the fact that no consistency exists in the type of immunological parameter measured. Verification of published data by cross checking for reproducibility between authors thus becomes virtually impossible. This is a major drawback in a field where the results are already confounded by problems in the quantification of the psychological stress, as well as in determining the perception and coping styles of animals. Other confounding factors include the comparison across biological host variables such as gender, age, species and strains of animals, seasonal differences, circadian differences and degree of adaptation, as well as psychosocial variables such as social status, social support, the presence and attitudes of significant others as well as the coping style and personality of the animal.

Other very important factors are the types and number of previous stressors that the animal was exposed to, i.e., the allostatic load of the animal - this could severely confound the results. Serious consideration should also be given to the characteristics of the applied stressor, including quantitative characteristics such as severity and duration and to the qualitative characteristics such as the type of stressor, time of day, the temporal relationship between development of the non-specific stress condition and the immune response, seasonal variations, frequency, and the controllability (avoidability/escape). Another factor that is often not planned with the necessary circumspection is that of the control group. In animals this issue might sometimes present with seemingly insurmountable problems as almost any form of handling may be perceived as stressful to some animals and inter-individual differences may be a real problem in constructing a uniform control group in terms of the experienced stress.

In conclusion, it can be said that a wide variety of factors can act as psychological stressors and in so doing have marked influences on the immunocompetence of animals. Any physical stressor able to provoke psychobiological arousal and the development of the nonspecific stress syndrome may lead to immunological alterations. The most generally observed immune effect is that of immunosuppression – an effect commonly associated with activation of the two main stress axes, i.e., the central noradrenergic/sympathoadrenomedullary axis and the corticotropin-releasing hormone/hypothalamo-pituitary- adrenocortical axis. It should, however, be remembered that the hypothalamus controls the secretion of other neurohormonal substances such as growth hormone, prolactin and endorphins which are known to exert immune stimulatory influences and that the two stress axes can, under certain conditions and in case of certain immunological parameters be immune enhancing rather than immune suppressive (18 & Chapters 4 and 5). The degree to which physical stressors will provoke psychobiological arousal is dependent on the qualities of the stressor, but also on the way the animal perceives the stressor. A multitude of psychosocial factors can act as, or rather, can be perceived or experienced as, stressors and thus may influence the immunological status. Some of the more relevant phenomena include (see Table 2.2)

- Social ranking, where dominance would appear to favour immunocompetence

- Appropriate housing conditions in the presence of significant others, where isolation, overcrowding, sex segregation and social disorder are often seen to predispose to infections and tumour growth.
- Appropriate infant-maternal bonding as well as the presence of significant others - which have been reported to be beneficiary to immunological competency. Separation, especially if the young are removed from familiar surroundings, has been shown to cause immune suppression that can sometimes be reversed upon reuniting. Of interest is the fact that the immunosuppressive effect of mother-infant separation appears to be carried through into adult life.
- Previous exposure to the same aversive event that may lead to sensitisation or habituation, to suppression or enhancement or even conditioned immune alterations upon cue presentation.

The one major factor that would appear to determine the immunological outcome of the stressor influence is the perception of the animal with regard to the stressor – and perhaps more specifically the perception of its ability to control or cope with the specific stressor. The perception of uncontrollability would generally lead to negative effects on the immune system. The distinction between the perception of controllability or uncontrollability, in turn, depends on the physical characteristics of the stressor, but also on the psychological characteristics of the animal, such as the ability to adapt, the coping style, personality traits, previous social interactions, previous stressor exposure, as well as on early maternal-neonatal and peer interaction (58,59,75,76).

2.3.2 Psychological stress and immune function in man.

Studies on the effects of stress on the immune system of man take a much closer look at real life situations than those on animals where the stressors are often either far removed from natural stressors and where the psychological experiences are difficult to interpret. The major types of stressors generally used in experimental designs for humans are

- Real life stressors such as separation, divorce, examinations, bereavement, care giving or illness in significant others, threatening illness, pre-operative stress, and unemployment

- Cumulative life stressors, i.e., the cumulative existential stress an individual experience over a period of time. Structured interviews and questionnaires are generally employed to assess the degree of cumulative stress and to compile stress scores
- Laboratory stressors such as problem solving and other cognitive tests, sleep deprivation, pharmacological interventions, temperature and noise exposure, and many other.

Psychoimmunological studies in man can usually be categorised into studies examining either acute or chronic stress. A large number of these studies involve some kind of psychometric testing or rating scale, i.e., state-dependent psychological assessments or personality testing. Examples of such assessments used include the Minnesota Multiphasic Personality Inventory, the Eysenck Personality Inventory, the Thematic Apperception Test, the Profile of Mood States, the State and Trait Anxiety Inventory, and others, as seen in Table 2.3.

Psychological assessment by means of rating scales, especially the self-scoring type of rating scale, although practical and inexpensive, are said to be inadequate characterisations of the psychological status (77). This statement becomes especially relevant in view of the refined technological procedures and high costs involved in the immunological assessments and neurohormonal profiles of the psychoimmunological studies.

An excellent compilation of psychoimmunological studies in man, over a twenty-one year period, was published by Bondi and Leonard, 1995 (77). Their work summarised the relevant information into experimental design, type of subject and degrees of freedom, psychological parameters or stressors, immunological asssessment, and results. The authors claims the publication to contain all major work on the psychoimmunological interaction in man over the specific period. This claim would appear to be justified. For this reason the compilation of Bondi and Pancheri (77) will, with minor adaptations and with written permission from the publishers, be reproduced here (Table 2.3). The studies are, where possible, subdivided into longitudinal prospective studies (serial assessments over time) and transversal studies (experimental versus control subjects).

The implications of the results in Table 2.3 are self-evident. It can be summarised by saying that there can be no doubt about the fact that a variety of stressors can inhibit the immune system. Contradictions do, however, exist. In the first place one has to distinguish between acute and chronic stress. (The difference between the effects of acute and chronic activation of the stress response is discussed in Chapter 5). Prolonged conditions of stress usually lead to immune suppression, while periods of acute and less severe stress cause minor or no immune suppression, and may even lead to immune enhancement. What is further needed, and had in fact been attempted by some, is to simultaneously assess the activity of the two main stress axes, the psychological scoring and the immune response. It is also very important that the perception of the individual about the stressor, its controllability and its aversive/appetitive qualities be assessed. The coping resources and coping style, as well as the personal needs of the individual are often among the most important factors that influence the perceptions of the individual and thus the neuroendocrine and immune status. Higher perceived stress is, for instance, known to be associated with higher cortisol secretion, while people in need of power show higher noradrenaline secretion when threatened, and in individuals with repressed coping increased endorphin levels have been reported (77). The type, concentration and period of high secretion of the stress-induced neurohormonal mediators would naturally be a major determinant of the immunological stress response.

Table 2.3: Evidence of stress-induced modulation of the immune system in man.

Design and reference	Subjects	Psychological Parameter or Stressor	Immune Assessment	Psychological Tests	Results
Transversal Canter, A. *et al*, 1972[1]	313 normal subjects 'vulnerable' vs 'non-vulnerable'	Perceived stress	Immunization tests	MMPI. CMI	Hypersensitive reactions to immunization more frequent in the vulnerable group
Transversal McClelland, D.C. *et al*, 1980[43]	27 college males	Inhibited power motivation	Secretory IgA	SRE	High scores in need of power, in inhibition, in reported power stresses are related to low S-IgA concentration
Transversal Biondi. M. *et al*, 1981	25 inpatients	Awaiting surgery	E rosette, PHA, skin tests	MMPI. STAI. Life events scale (SRE, LES), Scheme Reaction Test	Immuno-hyporactive subjects show suppressed emotional reactivity and higher denial
Transversal Baker, G.H.B *et al*, 1984[25]	61 students	Academic stress	T-helper	Visual Analogue Scale	High anxiety scores, high OKT4 cells
Transversal retrospective Locke, S.E. *et al*, 1984[44]	114 students (79 men and 35 women)	Life stress events Perceived stress	NK-cell activity	Life events scale, Hopkins' Symptom Checklist	Low perceived stress scores and high life stress events scores are related with high NK-cell activity
Transversal Kiecolt-Glaser, J.K. *et al*, 1984[12]	33 psychiatric inpatients	Loneliness	NK-cell activity, immune reactivity to PHA	UCLA Loneliness Scale, MMPI, Life Events Scale (LCS)	High loneliness group shows lower NK-cell activity and PHA response
Transversal McClelland, D.C. 1985[26]	46 students (29 men and 17 women)	Academic stress	Secretory IgA	Thematic Apperception Test	Increase in S-IgA
Transversal retrospective Thomas, P.D. *et al* 1985[25]	256 healthy elderly adults (54% men and 46% women)	Life stress events and social bonds	Total lymphocyte count, immune response to mitogens (PHA)	92-item self-rating scale of distress. Interview Schedule for Social Interaction (adapted to a self-administered questionnaire format)	Strong social support (defined in this study as satisfying confidant relationships) is related with higher lymphocyte counts and mitogen responses
Transversal Heisel, J.S. *et al* 1986[38]	111 students (78 men and 33 women)	Not considered	NK-cell activity	MMPI	High MMPI scores (T>70) are related with NK values below the sample median. Higher MMPI scales (Hy, D, Pd, Mf, Pa, Pt. Sc. Ma. Ego strength maladjustment) scores are related to lower NK-cell activity
Transversal Kiecolt-Glaser, J.K. *et al*, 1986[27]	34 students (22 men and 12 women)	Academic stress	T-helper, T-suppressor, NK-cell activity	Brief Symptom Inventory, UCLA Loneliness Scale	Decreased T helper numbers, T4/T8 ratio and low NK-cell activity on the day of examination

Design and reference	Subjects	Psychological Parameter or Stressor	Immune Assessment	Psychological Tests	Results
Transversal Kubitz, K.A. *et al*, 1986[39]	30 subjects	Perceived stress	Secretory IgA	Hassles Scale, Multi-dimensional Health Locus of Control Scale (MHLC). Profile of Mood States, Stress signal checklist, Stress coping rating scale	Secretory IgA levels inversely correlate with high internal locus of
Transversal retrospective Linn, B.S. *et al*, 1987[10]	24 healthy men undergoing hernia repair	Life stress events and pre- and post operative and surgical stress	Immune respons to mitogens (PHA, ConA, PWM	Not reported	High life events scores, high response to the cold pressure test, reduced immune response to PHA and PWM
Transversal Kiecolt-Glaser, J.K. *et al*, 1988[34]	64 men, 32 separated/divorced, 32 married	Separation / divorce	Antibody titres to Epstein-Barr Virus (EBV) and Herpes Simplex Virus type-1 (HSV-1)	UCLA Loneliness Scale, BSI, Dyadic Adjustment Scale (DAS), Life Events Scale, Kitson's Scale, Rotter's locus of control scale	Separated / divorced group vs married group: more illness reported in the former, higher antibody titres to EBV and HSV-1 (poor cellular immune system control over virus latency)
Transversal Jamner, L.D. *et al*, 1988[40]	312 outpatients classified as repressive (REP; n = 79), defensive high-anxious (DEF; n = 69) true high-anxious (HA; n = 124) and true low-anxious (LA; n = 40)	Not considered	Monocyte and eosinophil count	Marlowe-Crowne Social Desiderability (MC), Taylor Manifest Anxiety (Bending Form; MAS)	REP patients show lower monocyte counts than LA patients; higher eosinophil counts than LA and HA patients; more medication reactions reported than all other groups. DEF patients show lower monocyte levels than HA patients
Transversal Irwin, M. *et al*, 1988[13]	9 recently bereaved women; 11 anticipating death of husband; 8 controls	Bereavement	NK-cell activity	Not reported	Reduced NK-cell activity in bereaved women and in anticipatory bereaved women
Transversal Marchesi, G.F. *et al*, 1989[28]	14 students, 9 men and 5 women	Academic examination	T helper, T suppressor, T-11, T-3, NK and IL-2	MMPI, California Personality Inventory, Psycho-Somatic Inventory, Psychosomatic Experience Bank. Maudsley Personality Inventory, State-Trait Anxiety Inventory, Institute for Personality and Ability Testing, Anxiety Scale Questionnaire	6 students with high anxiety scores show decreased lymphocyte subsets

Design and reference	Sample	Psychological Parameter or Stresser	Immune Assessment	Psychological tests	Results
Transversal Brohee, D. *et al*, 1990[53]	9 normal subjects, 5 men and 4 women	Pharmacological stress (epinephrine and hydrocortisone intravenously)	T helper, T suppressor, T-11, T-3, NK and monocytes number immune reactivity to PHA. PMW, LPS	Not included	At 10 min increased all leukocytes, especially T suppressor and NK cells, at 1 h moderate lymphopenia and monocytopenia, at 6 h neutrophilia and eosinopenia, unchanged mitogen reactivity over all study
Transversal Levy, S.M. *et al*, 1990[14]	120 breast cancer patients	Life-threatening illness	NK-cell activity	A social support scale adapted for this study, Folkman and Lazarus Ways of Coping Checklist, Profile of Mood Scale, State-Trait Personality Inventory	High social support is related with high NK-cell activity and a good tumour status
Transversal Naliboff, B.D. *et al*, 1991[22]	23 women divided in two groups: young group (n = 12) and old group (n = 11)	Laboratory stress: mental arithmetic task and video taped lecture on a health topic	NK-cell activity and mitogen response (PHA), T-helper, T-suppressor and other lymphocyte subsects	Stress Symptom Ratings (SRR)	Increased T-suppressor and NK cells number in both age groups Increased NK-cell activity only in the younger group. No changes in T-helper number
Transversal Biondi, M *et al*, 1993[15]	50 normally healthy air crew	Life stress events, job stress, mood anxiety	Lymphocytes subsets, NK-cell activity	MMPI, STAI, Life Event Scale (QAV), Subjective Stress Questionnaire	Minor daily chronic stressors are not related to immune modifications: NK-cell activity positively correlated with social introversion: hypomania score negatively correlated with lymphocytes T-11 and NK-cell count
Transversal Brosschot, J.F. *et al*, 1992[16]	86 normal subjects; 50 experimental group; 30 control group	Three-dimensional unsolvable puzzle (experimental group), reading popular magazine (control group)	Mononuclear cell counts, lymphocyte subsets, immune response to mitogens (PHA, PWM and antigen cocktail)	General Health Questionnaire, Visual analogue scales for mood changes	Experimental subjects show increased Nk cells, T suppressors and cytotoxic cells after the stress period. No changes on the immune response to mitogens
Transversal Uske-Kirschbaum, A. *et al*, 1992[54]	24 students divided in three groups. Epinephrine controls, saline controls and conditioned	Conditioning procedure neutral sherbet sweet paired with a subcutaneous injection of epinephrine	NK-cell activity	Not included	Increased NK-cell activity in epinephrine and in conditioned groups. No changes in saline group

Longitudinal Studies

Design and reference	Sample	Psychological parameter or stressor	Immune assessment	Psychological tests	Results
Longitudinal Fisher, C.L. *et al*, 1972[2]	21 normal healthy flying crew	Space flight	Peripheral lymphocyte count, immune response mitogen (PHA)	Not included	Mean lymphocyte numbers and immune reactivity to PHA during spaceflight were in the normal range
Prospective Palmblad, J. *et al, 1976*[3]	5 normal subjects	Laboratory stress	Granulocyte phagocytosis and turnover	Not reported	Reduction in phagocytosis and higher turnover during stress followed by increment
Longitudinal prospective Locke, S.E. *et al*, 1977[41]	124 students	Perceived stress	Antibody titres to flu vaccine	Profile of Mood States, SRE	No relationship
Longitudinal, prospective Bartrop, R.W. *et al*, 1977[4]	26 bereaved subjects, 26 normal subjects	Bereavement	E, EAC rosette, PHA, ConA, Ig, T and B cells	Not included	Bereaved subjects show reduced PHA and ConA response
Longitudinal, prospective Greene, W.A., *et al*, 1978[45]	33 normal subjects	Perceived stress	Interferon, antibody titre, cytotoxicity	Profile of Mood States (POMS), SRE	Negative correlation between cellular immunity and LCU-Vigor score
Longitudinal, Palmblad, J. *et al, 1977*[47]	12 normal subjects	Sleep deprivation	Immune response mitogen (PHA) and polimorphonuclear Leucocyte number	Not included	Decreased immune response to PHA
Longitudinal, prospective Kasl. S.V.,*et al*, 1979[61]	1400 cadets	Academic stress in cadets	Appearance of EBV antibodies and/or mononucleosis	Demographic and psychosocial data	High academic motivation and poor performance predicted clinical mononucleosis
Longitudinal Totman, R. *et al*, 1980[17]	52 normal subjects	Life stress events	Antibody titre to experimental common cold	EPI, SRE	Introverts developed worse symptoms and infections than extroverts
Longitudinal, prospective Udelmann, D.L. 1982[18]	10 matched normal subjects	Under threat of loss	B and T counts	MMPI, Gottschalk Scale	Correlations with hope and antidepressants
Longitudinal, prospective Schleifer, S.J. *et al, 1983*[5]	20 normal subjects	Bereavement	B and T counts, PHA, ConA, PWM reactivity	Not included	Suppressed reactivity to PHA, ConA and PWM
Longitudinal, prospective Jemmott, J.B. *III et al, 1983*[29]	64 students (48 men and 16 women)	Academic stress	Secretory IgA	Thematic Apperception Test, Perceived Stressfulness Test	High perceived stress, low S-IgA level
Longitudinal, prospective Levy, S.M. *et al, 1985*[30]	75 breast cancer patients	Perceived stress	NK-cell activity	Not included	High distress is related with higher NK-cell activity
Longitudinal Kiecolt-Glaser, J.K. *et al, 1984*[37]	75 students	Academic examinations	NK-cell activity, IgA, IgM, IgG	Brief Symptom Inventory, SRRS, UCLA Loneliness Scale	NK activity decline under examination stress

Design and reference	Sample	Psychological Parameter or Stressor	Immune assessment	Psychological tests	Results
Longitudinal, prospective Irwin, M. *et al, 1986*[19]	39 women, 12 widows, 16 with ill husbands, 11 with healthy husbands	Husbands' disease, life stress events	NK-cell ativity	Ham-D Scale, SRS, General Health Questionnaire	High Ham-D scores and many life changes are correlated with impaired NK-cell activity
Longitudinal Taylor, G.R. *et al*, 1986[36]	41 astronauts	Space flight	Monocyte count, B-Lymphocyte count T-lymphocyte count T-helper number T-suppressor number, T-helper/T-suppressor ratio, Response to mitogen	Not included	Decreased monocytes, decreased B-lymphocytes, decreased T-lymphocytes, increased T-helper cells, T-suppressor cells slightly decreased, increased T-helper/ T-suppressor ratio, decreased T-cell blastogenic response
Longitudina lprospective Arnetz, B.B. *et al, 1987*[35]	3 women's groups, 9 unemployed women (group A), 8 unemployed women who received a psychosocial support (group b), 8 securely employed women (group C)	Unemployment	Lymphocyte stimulation tests (PHA, PPD)	Not included	Decreased reactivity of lymphocytes of PHA and PPD in groups A and B, no changes in the group C
Longitudinal Halvorsen, R. *et al, 1987*[37]	23 students, experimental group: 4 men and 7 women	Academic stress	Lymphocyte stimulation tests (PHA, IL-2, D. Farinae), T-helper number, T suppressor number, monocytes count, large T-helper number, large T-suppressor number	State-Trait Anxiety Inventory, 10-point analogue scale	During acute examination stress: increased monocytes, decreased large lymphocytes T-helper and T-suppressor, no changes in the T-helper and T-suppressor, total number reduced response to IL-2. After the examination: Reduced response to antigen (D. Farinae) and mitogen (PHA)
Prospective Tonnesen, E, *et al*, 1987[11]	20 inpatients	Coronary artery bypass grafting	Lymphocyte subsets, NK-cell activity immune response to mitogens	Not reported	Increased of NK-cell activity while awaiting for surgery; decreased postoperatively: decreased immune response to PHA
Longitudinal, Ironson, G, *et al, 1990*[20]	46 gay men and 25 controls	HIV-1 antibody status notification	T-helper, T-inducer subset and NK cell numbers; immune response to mitogens (PHA, PWM); NK-cell activity; HIV-1	State-Trait Anxiety Inventory (STAI), Impact of Events Scale (IES), Life Experience Survey (LES)	Seropositive subjects show increased anxiety, high avoidance and intrusion scores (IES), decreased NK-cell activity at the time of seropositive status notification and 1 week later an unchanged immune response to PHA and PWM. Sero-negative subjects show depressed immune response to PHA and PWM at the baseline evaluation. At 5 weeks measures returned to base line in both seropositive and seronegative groups.

Design and reference	Sample	Psychological Parameter or Stressor	Immune Assessment	Psychological Tests	Results
Longitudinal, Fawzy, I. *et al*, 1990[8]	61 patients with malignant melanoma (28 men and 33 women) divided in two groups: controls (n = 26) and psychiatric intervention patients (n = 35)	Cancer diagnosis, coping and effective state	T-helper. T-suppressor, NK cell and Large Granular Lymphocytes number. NK-cell activity	Profile of Mood State (POMS); Dealing with Illness – Coping Inventory	At 6 weeks intervention group vs control group shows higher anger, low anxiety and depression related with higher LGLs and NK-cell percentage and NK-cell activity. At 6 months the difference between the groups remains.
Longitudinal prospective Fittschen B. *et al, 1990*[32]	61 students	Academic stress	Large immunocytes number (LI); antibodies titre against Herpes Simplex Virus (HSV)	Not reported	No changes in HSV-Ab over all subjects; increased LI percentage; high perceived stress is related to higher antibody titre.
Longitudinal prospective Biondi, M. *et al, 1994*[42]	24 normal subjects	Life stress events, mood, anxiety	NK cell, lymphocyte T-helper, T-suppressor, T-11 count: NK-cell activity	MMPI Life Event Scale (LES, SRE), STAI, Subjective Stress Questionnaire, Reactive Scheme Test	At 1 year increases in depression, demoralization, social introversion and a decrease in perceived social support are associated with significant reduction in lymphocyte T-11 percentage.
Longitudinal Glaser, R. *et al, 1992*[33]	48 medical students (25 men and 23 women)	Academic examinations and HepB vaccine injection	Antibody titres to HBsAg and blastogenic response to HBsAg peptide (SAg)	Profile of Mood States (POMS), Perceived Stress Scale (PSS), Interpersonal Support Evaluation List (ISEL)	Early seroconvertors (seroconverted after the first vaccine injection) are lower in anxiety and perceived stress levels than later seroconverters. At the third vaccine innoculation high social support scores are related with higher antibody titres and blastogenic response to SAg.

In examining the effect of various stressors and thus by implication the effect of the non-specific stress response on the immunological defense mechanisms one is stimulated to approach the interaction from the reversed point of view. This alternative view would be to look at excessive immunological activity as a stressor model in its own right. In its activity as a disturbance of the internal homeostasis one could very well consider

pronounced immune responsivity as a stressor. Conceptualisation of antigens as stressors have indeed previously been proposed by others (78,79). This approach would be in good agreement with the fact that immune-derived cytokines can elicit the general adaptation syndrome by central stimulation of the two major stress axes. The fact that the immune system can influence the two major stress axes has, in fact, been known for a long time and was even, in a practical way, confirmed during World War 1 when it was noticed that fatal infections can lead to striking morphological changes and functional alterations of the HPA-axis (80). The mechanisms through which the immune system can influence the brain and behaviour will be discussed in Chapter 6.

It has also been said that the evidence for a negative role of stress on health can be observed much better from the association between stress and illness behaviour (symptoms and the use of medical facilities) than for the association between stress and objective pathology (81). This, to a degree, makes sense if the role of immune-derived cytokines in the development of sickness behaviour is taken into consideration. (The link between cytokines and sickness behaviour is discussed elsewhere in the thesis.) However, despite the relative merits of the above statement, there can be no doubt that psychological stress can be severely detrimental to the immune system and may even render the individual fatally vulnerable to infections.

2.4 Other interesting associations between the immune system and behaviour

It is not possible to include examples of all conditions in which a psychoimmunological link has been reported. This section will briefly discuss a couple of interesing conditions merely to show that the interaction is not unique to the condition of negative stress.

It is common knowledge that a sense of humor can alleviate stress and that laughter involves an emotional state almost opposite to that of bereavement and sorrow or even anger or anxiety. It is postulated that the supplementary motor area of the cortex contains a site which, when activated, produces laughter (82). When stimulated this area sends inhibitory signals to the structures involved in sympathetic nervous system activation and in the activation of the HPA-axis with subsequent decreases in plasma cortisol and

cathecholamine levels (83). By decreasing levels of stress hormones it is feasible that laughter can be beneficial to the immune system. This assumption has been supported by other reports (84), but more work is necessary to absolutely confirm it.

Belief systems such as religious and other spiritual activities are said to be able to counter or partially counter the effects of stressful environmental conditions on the immune system. This, however, depends on how the individual really experiences these spiritual activities and the manner in which he or she partakes in the associated activities. Studies on humans include

- A comparison in cancer susceptibility and development in Mormon men strictly adherent to church policies and Mormon men not always adhering to the policies (85). The risk of cancer development was shown to be significantly lower in the strictly adhering group of Mormon men. It goes without saying that the results may have been of an epiphenomenological nature.
- A similar comparison, with similar results, between Dutch Seventh Day Adventists and the general Dutch population (86).
- A study on the differences between Israeli secular and religious kibbutzes, where the health-related mortality rate was about twice as high in the secular kibbutzes (87).
- Higher IL-6 levels in church going elderly individuals than those not regularly attending church (88).
- Indications that subjects practising transcendental meditation are healthier and that their better general health is based on lower activities of stress hormones (89).

The most obvious explanation for the above is probably the type of social interaction and other factors that reduce stress activation and thereby immunosuppresion, but the placebo effect may also be involved.

2.5 Mental disturbances and behavioural traits as examples of the psycho-immunological interaction.

Popular associations as well as substantial literature suggest a link between certain psychological traits as well as a number of psychiatric disorders on the one hand, and the immune system on the other. The existence of such associations is witnessed, amongst others, by

- The immune alterations reported in depression and schizophrenia.
- The implied association between viral aetiology and psychoses and between viral aetiology and affective disorders.
- The increase in neurodevelopmental schizophrenia subsequent to major influenza epidemics.
- The postulated link between chronic viral infections and the chronic fatigue syndrome with its mood disturbances.
- Mood disturbances in certain autoimmune diseases.
- The concurrent mood and immunological disturbances seen in certain neurodegenerative diseases.
- The psychological behaviour known as sickness behaviour that occurs in association with infectious conditions.

A discussion of the above, as well as the necessary references can be found in Chapter 7.

With a more in depth examination of recent publications it becomes clear that immune involvement is probably present in most, if not all, psychiatric disturbances and that it may even be involved in the development of many psychological dispositions and traits. The validity of this statement will be supported by examples provided in the following couple of paragraphs. It is evident that a discussion or even the mentioning of all available examples are far beyond the scope of this thesis. Examples will therefore be supplied for the various categories with more emphasis on those associations that have been under wider scientific scrutiny. The order of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (90) will be followed to roughly systemise the psyciatric disorders and related psychological dispositions and traits. It may not be

strictly correct to group psychopathological and non-pathological phenomena in this way. It does, however, serve as a convenient arrangement in order to provide the necessary examples in support of the statement made at the beginning of this paragraph. A comprehensive search has been performed for immune involvement in all categories of the DSM-IV classification and abstracts are available on a series of discs. It is, however, self-evident that the work involved in completion of such a study would be endless and further analysis of the information is thus envisaged only after completion of this thesis.

Examples from each of the DSM-IV categories are provided in the following order:

2.5.1 Disorders usually first diagnosed in infancy, childhood, or adolescence
2.5.2 Delirium, dementia, and amnestic and other cognitive disorders
2.5.3 Disorders due to a general medical condition not elsewhere classified
2.5.4 Substance-related disorders
2.5.5 Schizophrenia and other psychotic disorders
2.5.6 Mood disorders
2.5.7 Anxiety disorders
2.5.8 Somatoform disorders
2.5.9 Factitious disorders
2.5.10 Dissociative disorders
2.5.11 Sexual and gender identity disorders
2.5.12 Eating disorders
2.5.13 Sleep disorders
2.5.14 Impulse-control disorders not elsewhere classified
2.5.15 Adjustment disorders
2.5.16 Personality disorders
2.5.17 Other conditions that may be a focus of clinical attention

2.5.1 Immune involvement in disorders first diagnosed in infancy, childhood, or adolescence

The prevalence of immunological alterations in disorders first diagnosed in infancy, childhood and adolescence is of such a magnitude that a plea, based on scientific

evidence, was recently made for immune-based strategies in the study and therapy of childhood neuropsychiatric disease of this DSM-IV category (91). Examples include

- abnormal cytokine profiles in the cerebrospinal fluid of children with obsessive-compulsive disorders, attention deficit hyperactivity and childhood-onset schizophrenia (91).
- low natural killer cell activity in conduct disorder (92), stuttering and other speech impediments, as well as attention-deficit and reading problems in children of mothers with systemic lupus erythematosis. Results of the latter study imply excessive maternal immunoreactivity to be a risk factor for learning disabilities in their offspring. This indirectly supports the immunoreactive theory of Gualtieri and Hicks which hypothesised the higher prevalence of childhood neurodevelopmental disorders in males to be the result of male fetuses being more antigenic to mothers, with subsequent increased immunological effects on the developing brain (92).
- the link described between immune disorders and language disorders by the Geschwind-Behan-Galaburda model of cerebral lateralisation. This is at present still strongly debated, but serious support for the theory can be found in the arguments of certain research groups (93).
- defective T-cell immunity reported in Schimke immuno-osseous dysplasia, a pleiotropic disorder with cerebral infarcts and mental retardation (94). The magnitude and clinical importance of the immune involvement is, however, not yet clear.
- the psychoimmunological associations proposed for autism. Two related conceptual frameworks are described, a viral and an autoimmune hypothesis (95).

Many other examples can be found where an abnormal immune status in either the child or the expecting mother is implicated in developmental problems of this class of mental disorder. An integrated review of all available information is urgently needed to establish the role of the immune system in the various disorders first diagnosed in infancy, childhood or adolescence. At present there can be no doubt that immune disorders are present in many of these patients. A serious attempt should, however be made to determine whether immune disturbances are the primary determinants of the mental

disturbances or whether adverse life events activate the stress response which in turn leads to immune alterations.

2.5.2 Immune involvement in delirium, dementia, and amnestic and other cognitive disorders and episodes.

The major part of work applicable to this category is the cognitive disturbances secondary to the development of HIV/AIDS and Alzheimers dementia. However, abnormal immunological activity has been reported in almost all subdivisions.

Recently a host of studies added to our knowledge on possible immunological mechanisms contributing to the cognitive dysfunction of disorders such as Alzheimer's. The following represent just some of the published results.

- Antiphospholipid antibodies (aPLA) are implicated in the focal ischaemia and diffuse brain damage of dementia (96)
- Immunological events may play a role in vascular dementia (97).
- The neuropathogenesis of Alzheimer's disease is strongly suggested to revolve around the immunological activation of glial cells with subsequent inflammatory neurotoxin production, neuronal injury and neuronal demise (98).
- Augmented intrathecal release of pro-inflammatory cytokines such as tumour necrosis factor-alpha and interleukin-1-beta are reported in a variant of Creutzfeldt-Jakob disease (99).
- It is fairly well accepted that the immune system plays a role in the development of Alzheimer's dementia. What is perhaps less well known is that the immune system may also be a contributor to the defense against the cerebral changes that underlie the dementia. The development of Alzheimer's dementia is considered by some to be an imbalance between the two immunological mechanisms resulting from the failure of the defense mechanisms. In short, inflammatory proteins such as enzymes, complement, cytokines, as well as the eicosanoid mediators, found in association with the glial cell-derived amyloid plaques, are said to stimulate the formation, aggregation and cytotoxicity of amyloid beta. Microglial cells, in contrast, have been shown to degrade amyloid beta and amyloid beta-specific T cells to aid in the elimination of the

peptide. The latter two mechanisms are said to be defective with the development of Alzheimer's disease (100).

- Chronic inflammatory processes with subsequent neuronal loss and dementia have been shown for other neurodegenerative disorders such as Parkinson's disease, and amyotrophic lateral sclerosis. Of interest is the fact that epidemiological studies with patients on anti-inflammatory drugs showed a remarkable reduction in the prevalence of dementia and, in some afflicted individuals, even a total arrest of disease progression (101).
- Pathological activation of microglia with the subsequent release of toxic oxygen radicals, nitric oxide, peroxynitrites and neurotoxic cytokines have been shown to give rise to secondary activation of astrocytes that results in loss of their differentiated state. This loss of differentiation impedes functions such as extracellular glutamate and potassium uptake, as well as the production of neurotrophic factors. This, in association with the effect of the previously mentioned pro-inflammatory cytokines could lead to a pathological imbalance of calcium and cyclic-AMP-dependent signaling which, in itself, can lead to further dysregulation of glial function with augmentation of amyloid deposition, release of neurotoxic substances and inhibition of neurotrophic factors (102).
- Overexpression of S100B, a multifunctional unit of the S100-calmodulin-troponin superfamily of proteins and S100B-specific T-lymphocytes are implicated in Alzheimer's and in several other disorders where cognitive abnormalities are known to be present (103).
- The brain inflammatory response, as mentioned in the above examples is also implicated in the susceptibility of Alzheimer's patients to delirium (104).
- A neuro-autoimmunity model involving a CD8+ cell-mediated mechanism is further said to contribute to the neurodegeneration of Alzheimer's disease (105).

Various other examples of immune involvement in Alzheimer's, Creutzfeldt-Jakob, vascular, multi-infarct and other dementias exist, but the above examples should suffice as convincing evidence that inflammatory and therefore immunological responses and perhaps even autoimmune activity are likely to be major contributors to the cognitive disturbances.

Acquired immune deficiency syndrome (AIDS), the later stages of the immunodeficiency virus (HIV) infection, is marked by a variety of neuropsychiatric symptoms. Included are mood disturbances (major depressive, dysthymic and bipolar disorder), and the progressive cognitive impairment known as the AIDS dementia complex (ADC). The ADC involves prominent psychomotor slowing, problems with concentration and memory and may progress to severe dementia, mutism, incontinence, paraplegia and even myoclonus. Psychological symptoms such as psychoses and personality changes may, however, also present during the earlier stages of the disease (106).

It is generally accepted that the viral and cellular products from immune competent mononuclear phagocytes underlie the neuropathogenesis of HIV-1 associated dementia. Pro-inflammatory chemokines and chemokine receptors are among the immunological factors implicated in the development of central nervous system inflammatory disorders and HIV-associated dementia (107). Far less is, however, known about the neurodegenerative nature of HIV-infections than about the previously mentioned conditions. Much of the very recent work still awaits further clarification and confirmation and will thus not be discussed any further. The association between the psychological and immunological aspects of HIV will, in the next paragraph, rather be looked at from a different point of view.

It can with a fair degree of certainty be assumed that immune alterations may be instrumental in some of the behavioural symptoms of HIV/AIDS. Indications, however, also exist that the psychological disposition may influence the immunological expression. The various lines of evidence that address the possibility of a relationship between the psychological status and the disease progression in HIV infection can be summarised into two approaches. The first approach which deals with the possibility of psychological disposition as prognostic indicator, and the second which deals with the effect of psychological destressing interventions on immunological status and disease progression. The latter is based on the assumption that immune suppression by psychological stress would increase the immunological vulnerability to the development of full-blown AIDS.

The effect of psychological intervention on disease progression in HIV infected individuals is relatively well studied – considering the short period since HIV/AIDS became considered a major threat. The results of mind-body psychotherapeutic interventions in AIDS patients appear to be promising with regard to psychological well-being and indications are that physiological advantageous effects such as buffering of the CD4 decline, an increase in the NK-cell numbers and slower disease progression may also result from these interventions (108,109). Long-term studies with greater degrees of freedom are, however, necessary to properly evaluate the situation.

Psychosocial factors that were studied as possible prognostic indicators of disease progression, and by implication immunological incompetence, in HIV/AIDS include mood, coping strategies, negative expectations and optimism, social support or loss of social support, spirituality and religiosity, as well as personality traits such as commitment, control, openness about the disease and about sexuality, *versus* concealment, and hardiness (108,109). Individuals with negative expectations, irrespective of treatments such as AZT, are said to show poorer results with regard to the immunological factors indicative of disease progression (CD4 counts, proliferative responses, neopterin levels, β2-microglobulin concentrations) than individuals with the so-called self-orientated, active-optimistic coping behavioural pattern. Bereavement and loss of social support were found to be of reasonable prognostic value as both were seen to be associated with an almost uniform decline in immunological defenses. Religion and spirituality generally showed positive correlations with a more favourable prognosis - only under conditions of active, harmonious involvement. In contrast, existential loneliness, associated with problems with faith and religion seems to have negative effects. In investigations which tried to find prognostic personality traits, better immunological and disease progression outcomes were noted in association with conscientiousness and a sense of commitment and control. The prognostic value of depression seems to vary, but at this stage it appears safe to say that severe, chronic depression – unrelated to bereavement – may be accompanied by a more rapid decline in CD4 counts, and, by implicaton, a poorer prognosis. Active coping strategies, including active confrontation, openness about the disease, distraction and active avoidance of obsessive rumination, are generally seen to be associated with a better prognosis than the

less active strategies such as denial, fatalistic acceptance, or even what appears to be realistic acceptance (108,111). We have recently published a short article, which deals with the effect of the psychological disposition on the progression of the disease (108).

In the previous paragraphs the probability of a role for immune alterations in the development and maintenance of cognitive dysfunction were provided by a number of examples, including Alzheimer's disease and AIDS. It was also shown that psychological phenomena such as the perception of control, spirituality and coping strategies can influence the clinical disease progression. However, immune involvememt in many other examples of dementia, amnesia, delirium and other cognitive dysfunctions are available. Despite the emergence of more and more evidence for the psychoimmunological interaction in disorders of this group of the DSM –IV classification, the significance is not yet clear and the time has perhaps come to look past the minute detail in order to find the integrated pattern

2.5.3 Immune involvement in mental disorders and dysfunctions due to general medical conditions not elsewhere classified

A link between psychological disturbances and mental disorders due to general medical conditions not included in the previous classifications, is perhaps most evident in the autoimmune diseases. Autoimmune mechanisms which may obviously influence the brain include the development of anti-cerebral antibodies or anti-neurotransmitter receptor antibodies, but other mechanisms such as those that cause major cytokine disturbances could potentially also influence the behavioural functions. The reverse is, however, also true, i.e., that behavioural phenomena can influence cytokine production - as shown in later chapters. Depressive symptoms and disorders are among the major behavioural changes seen with autoimmune disorders and chronic inflammatory disorders. The severity and prevalence of the depressive symptoms are often of such magnitude that patients are frequently hospitalised with a diagnosis of depression rather than with a diagnosis of an autoimmune disease or chronic inflammatory disorder. It is therefore difficult to decide where to classify such patients in the DSM-IV system. Although the high incidence of depression in physical disorders of this type may be secondary to the chronic disability and pain that accompanies many such diseases,

indications are that autoimmune activities may very well be the causative factor for certain types of depression. It has even been suggested that patients with primary depressive disorders should be examined for anti-brain autoimmune reactions. The search for autoimmune markers such as rheumatoid factor, antinuclear antibodies, antimitochondrial antibodies, antibasement membrane antibodies, antithyroglobulin antibodies, anticardiolipin antibodies, levels of soluble interleukin-2 receptors and lupus anticoagulant, had mixed success in patients hospitalised with neuropsychiatric disorders, and the picture is still far from clear. (112).

Strong scientific support exists for a link between a number of neuropsychiatric disorders and conditions that are either confirmed autoimmune diseases or where autoimmunological processes contribute to the pathology. The major examples of this psychoimmunological link include myaesthenia gravis, Guillian-Barre syndrome, multiple sclerosis, paraneoplastic cerebellar degenerations, Huntington's chorea, Sydenham's chorea, Parkinson's disease and systemic lupus erythematosis (SLE) (112,113,114,115, 116). The associated mental disturbances show strong inter-individual, as well as chronological, variation in intensity and pervasiveness and are often only present during attacks. In some of these disorders, for example SLE, the initial symptoms may be psychiatric and the presence of the autoimmune nature of the disease may be overlooked. This, in case of SLE, is not surprising, considering the most common mental disturbances associated with the neuropsychiatric attack of SLE, i.e., inattention, disorientation, memory impairment, perceptual problems and, on occasion, hallucinations and schizophrenia-like symptoms.

Systemic lupus erythematosus (SLE), seen, in general medical terms, as an autoimmune disease, and by the DSM-IV classification as a personality change due to a general medical condition, is a good example of the psychoimmunological interaction. SLE can be accompanied by psychiatric manifestations such as psychosis, delirium, depression, dementia and those symptoms already mentioned in a previous paragraph. Immunological involvement is evidenced by the presence of antinuclear and anti-deoxyribonucleic acid antibodies as well as lupus anticoagulant, anticardiolipin antibodies and other immunological alterations (115).

Another autoimmune diseases in which neuropsychiatric manifestations may strongly resemble that of a primary mental disorder include Sydenham's chorea which is characterised by emotional lability with fits of crying or temper tantrums, and sometimes a psychosis.

Other medical examples in which immunological and mental disturbances co-exist are the demyelinating disorders, as seen in the previously mentioned condition of multiple sclerosis (MS). MS is said to cause delirium, dementia and non-affective psychoses, mood disturbances (major depressive disorder, bipolar syndromes, euphoria) (116), as well as the memory impairment and inappropriate behaviour referred to in an earlier paragraph. MS is probably one of the best examples of the bidirectional interaction between immunological activity and neuropsychological activity. Immunologically MS is characterized by multiple inflammatory and demyelinating lesions. The immunological alterations include factors such as multiple inflammatory foci, abnormalities in IgG production, as well as cell-mediated and other immune responses to myelin antigens. Opinions vary as to the primary etiology, but related mechanisms such as a viral influence in susceptible individuals, a retrovirus which encodes a super-antigen capable of stimulating T-cell dependent immune responses, and a virus which may provoke an immune response by molecular mimicry of the supposed antigen are considered (117). Although classified primarily as a demyelinating neurological disease, MS is recently becoming accepted as a chronic inflammatory disorder and even, by some, as an autoimmune disorder (117,118).

Psychological influences such as stress are described as contributors to both the development and the progression of some of the autoimmune diseases. The existence of a positive correlation between emotional pathology and the development, progression and relapse of MS and other autoimmune disorders is supported by many publications, but some controversies still exist (117).

It is, however, not only in autoimmune disorders where a link has been proposed between immunology and behaviour. Several studies indicate that the anhedonic effects

of various medical conditions are caused by immune-derived cytokines. If this is true, it becomes a waste of time to study individual diseases in terms of psychoimmunological interactions. What then becomes necessary is to decipher the general effects of the various cytokines on the behavioural processes, the cytokine profiles of the various disorders, as well as the cerebral mode of action of the various cytokines. An attempt to this effect is made in Chapter 6.

2.5.4 Immune involvement in substance abuse and substance related disorders

The link between substance abuse-related disorders and immune function speaks for itself if one considers the evolvement of independent, but related disciplines such as psychopharmacology and immunopharmacology. Examples of immune suppression through drug abuse, including, carbamazepine, heroin, alcohol (119) and inhalant (120) abuse, can be found throughout the literature. In view of the fact that the immunological effects of several drugs of abuse are fairly well known, and that this is not directly related to this dissertation, no further discussion is warranted on the cause-and-effect from a drug-to-immune direction. Whether immunological factors can predispose to substance abuse remains to be seen. What will however, be seen in Chapter 5 is that part of the CRH system plays a role in the vulnerability to drug abuse. In Chapter 6 it is shown that this system is influenced by immunological activity.

2.5.5 Immune involvement in schizophrenia and other psychotic disorders

The best investigated association between mental disturbances and the immune system is probably that seen in the major psychoses such as schizophrenia. The reason for this is that immune alteration - be it in the form of an autoimmune disturbance, or as a defense against viruses – is, in certain circles, thought to be the primary cause of a number of psychotic conditions. Although immunological alterations have been associated with schizophrenia since the 1930s, no absolute conclusion has been reached as yet. This can partially be ascribed to the heterogeneity of the disease and the fact that the classification according to the DSM-IV and that according to biological markers do not correspond.

The major points of view with regard to the association between schizophrenia and the immune system could probably be divided into the concepts of schizophrenia as an

autoimmune disease, schizophrenia as a genetic disturbance localised in the HLA system on chromosome 6, and/or schizophrenia as an immune alteration secondary to viral infections (121). The three approaches are obviously not necessarily mutually exclusive.

The results of individual immunoassays in schizophrenia generally show, despite some contradictions, an increased immune activation (121). The increase in immune activation would appear to be secondary to a defect in the suppressor functions of the immune system. In this and other aspects the picture corresponds to that of several autoimmune diseases, including systemic lupus erythematosis and multiple sclerosis. There are also indications that the reduced suppressor function in schizophrenics could be related to a deficiency in a specific type of cytokine, i.e., interleukin-2 (122,123,124,125,126) This is yet another characteristic shared by a number of autoimmune diseases (126). Other factors that appear to be common to both schizophrenia and autoimmune diseases are hyperactivity of the B-cell system and loss of suppressor cells (121). Some positive correlations exist between the degree of immune activation and the psychopathology of the disease, including the duration, a positive family history, schizophrenic symptomatology and responsiveness to neuroleptic treatment. A significant amount of work has been performed on the CSF content in schizophrenia. Interesting results include the increase in protein content, particularly in IgG content, which could be indicative of occurrences such as an increase in the blood-brain barrier permeability or a cerebral inflammatory process. Here again we see the non-specificity of correlates as the same type of situation is seen in purely physical inflammatory conditions such as the systemic inflammatory response syndrome (SIRS) and septicaemia. These conditions, by the way, are also sometimes accompanied by transient disturbances in consciousness. Correlations between the Munich version of the Scale for the Assessment of Negative Symptoms (SANS) and CSF IgG levels show statistical significance (127). The SANS consists of 5 subscales of symptom complexus, i.e., affective flattening/affective blunting; alogia/paralogia; avolution/apathy; anhedonia/asociality and attentional impairment, as well as a total score. Although not proven, such results would be compatible with a possible viral aetiology. For recent opinions on the association between the immune system and schizophrenia, the reader is referred to a review which shows that both innate

and the aquired immunity is altered and that the immunological picture is markedly changed by antipsychotic treatment (128).

The idea of a viral aetiology for schizophrenia was originally derived from studying family and epidemiological histories. These studies provided some interesting information, including

- The association between winter-born and a higher incidence of schizophrenia (129)
- The association between the incidence of schizophrenia and geographical distribution (130)
- The occurrence of psychotic symptoms in conditions of viral infections such as herpes simplex encephalitis, varicella zoster encephalitis and subacute sclerosing panencephalitis (121)
- A high incidence of schizophrenia in children born of mothers who, during the gestational period, were infected by the influenza virus during the 1957 epidemic in England (131)
- The high serum and CSF titres of anti-viral antibodies in conditions of schizophrenia. Many workers could not substantiate such claims (121). However, the same pattern of appearance and disappearance of antibodies are reported for multiple sclerosis and other medical conditions, and may be a reflection of the disease pattern rather than a contradiction of results.

As genetic inheritance is assumed by many it is natural that the HLA system should have been investigated in schizophrenics (121,132). The majority of studies concentrated on the HLA-1 antigens and results are fairly inconsistent. Some of the inconsistencies seem to be related to the differences associated with variations in family history, race, symptomatology and co-morbidity of other psychological disturbances. The results on HLA-2 looks somewhat more promising but much more work is required before an absolute conclusion can be reached.

In summary it can be said that little doubt remains about a link between schizophrenia and immune alterations, and that the possibility of an epiphenomenological occurrence is

remote. What is less feasible is the possibility that the immune alterations be as specific a correlate of the disturbance as would appear on first scrutiny. The final conclusions will, however, probably not be reached without first redefining the subclasses of schizophrenia and other psychotic disturbances.

2.5.6 Immune involvement in mood and mood disorders

The connection between mood and immune status has been noticed long before any knowledge of the existence of an immune system. Galen (200 AD) already commented on the fact that melancholic women are more susceptible to breast cancer than their so-called sanguine counterparts. Today it is fairly well accepted that a personality type can be associated with a high susceptibility to cancer – the type C personality. More about this at a later stage.

Over the last decade scores of studies supported the idea of immune disturbances in patholocial depression. However, a detailed discussion on the immunological alterations is, at this stage, beyond the scope of this writing and more attention will therefore be directed to the proposed mediating factors between depression and immunity. In this respect it can be said that the interphase between the mood disorders and immune status would appear to be directly in line with the psychoneuroimmunological concept.

When examining various publications, the results of numerous measurements point towards an immune suppression during depression (133). The picture does, however, change when the results of studies examining the functional activation state are considered. By examining the activation status it would appear that, despite the apparent immune suppression, a general activated state is present. This impression is in agreement with the argument of Maes, Smith and Sharp, 1995 (134), that major depression is associated with immune activation reminiscent of an acute phase response. The assumption is supported by Maier, Watkins and Fleshner, 1994 (135) who found macrophage activation in depressed patients. As macrophages with their associated major histocompatibility complex (MHC) characteristics form an important component of the circulating antigen presenting cell pool, one is reminded of the fact that the same mechanism is speculated to be of primary importance in the psychoimmunological link

seen in psychological conditioning of the immune system. The idea of the immune disturbance of depression being an immune activation with an eventual co-existing subnormal immune responsivity is tempting as it corresponds to the picture seen in certain chronic inflammatory disorders where patients are eventually known to exhibit immune incompetence – despite, or rather due to chronic stimulation. This would then, in fact, represent yet another form of a non-HIV acquired immunodeficiency syndrome. Of interest is the fact that such a situation would be in strong support of the idea that a particular pattern of immune suppression or alteration could not be seen as a specific correlate of depression.

Abnormalities of noradrenaline and cortisol are known neuroendocrinologal disturbances of depression. It is interesting that both systems are also able to influence the immune system and are influenced by immune system-derived cytokines. The details of this bidirectional influence will be discussed in later chapters. Enough at this stage to say that this interaction has been implicated in the sickness behaviour associated with inflammatory conditions and with infective diseases (136).

It is perhaps necessary to momentarily dwell on the reason for the existing discrepancies in research results. It is obvious how the earlier referred to co-existence of immune activation and immuno-suppression can lead to discrepancies in the findings from different populations. It is well known that various research groups use different immunological parameters to assess immune activity and, depending on the tests used, different conclusions may be reached. Other factors which can influence the immune status of the depressive individual and which, without doubt, could have contributed to the contradictions in results include a) subject characteristics such as age, gender and individual stress levels, b) the depression characteristics of the subjects such as ambulatory status, depression severity, depression subtype, neurovegatative symptoms, nutritional status and eating patterns, sleep disturbances and circadian phase shifts, and c) co-morbidity including anxiety disorders, alcohol dependence, tobacco dependence as well as psychotic symptoms, personality disturbances and others. All of the above are known to independently alter the immune status. The impact of some of these factors in the determination of the immune status in depressed individuals has recently been

reviewed (137). Major deficits in most of the research protocols would seem to be finer discrimination between the types of depressive illnesses, the duration and the continuity of the depression, as well as the recording of the type and number of criteria for depression present. Other confounding factors inherent to many research protocols include a) the heterogeneity between patients and controls, b) the variability of the immuno-assays used and the non-reproducibility from laboratory to laboratory, c) the relevance of the type of immunoassay to the information required, as well as, d) the perception and cooperation of the individual being assessed (133,138).

An important point made by Irwin (138) is the fact that converging evidence suggests that the immune alterations of the major depressive state may not be a specific correlate of depression, but could probably be found in stress and in other conditions of mental disturbances. This phenomenon has been referred to in the discussion of the psychoimmunological link seen in psychotic conditions. For any one involved in the medical side of immunology it would be clear that some correspondence in the immune alterations could also be found in a number of unrelated medical conditions. A common behavioural or biological denominator or denominators, shared by various mental states, and, in fact, probably by physical disturbances too, could thus possibly be the causative denominator/s. In examining the diagnostic criteria for the diagnoses of mood disturbances it is obvious that many of them are also present in biological disturbances associated with immune activation. Depression has, in addition, been shown to be accompanied by an acute phase response, as well as by increased secretion of prostaglandins and other pro-inflammatory mediators (137, 139) - very similar to that found in a number of medical conditions. The latter again illustrates the non-specificity of the behavioural and immune responses of the mood disorders.

The macrophage theory of depression is based on the fact that macrophage activation can increase the secretion of glucocorticoids, a) by secretion of cytokines, especially the pro-inflammatory cytokine interleukin-1 which stimulates the release of CRH, and through the secretion of ACTH by the macrophage itself. Macrophages can thus directly as well as indirectly lead to hypercortisolaemia (138). Cytokine production by macrophages may in itself underlie some of the depressive effects. The effects of cytokines on the brain and

on the behavioural functions will be discussed in Chapter 6 and the role of CRH and glucocorticoids in chapter 5. An interesting point, not mentioned in the macrophage hypothesis, is the fact that the macrophage theory can probably be expanded to the MHC class 2 antigens – molecules that have previously been suggested as factors in the psychoimmunological link in occurrences like conditioning, stress and other mental events. This again ties up with cytokine production as functional MHC antigens on macrophages are essentail for the initiation of the process that stimulates cytokine production.

When looking at the interaction from a reversed point of view, recent work seems to offer some explanation for previous contradictions. The general earlier consensus was that depression is uniformly associated with immune depression and the results from a couple of reports that could not support this were questioned. It would now appear that clinical depression suppresses, while subclinical depression may initially enhance immune function (140).

The following points represent an attempt to come to some kind of conclusion on what is presently known about the psychoimmunological interaction in mood disorders, and on the possible interface between the altered immune status and depressive states of mind. Thus, without pre-empting the more mechanistic descriptions of chapters 3, 4, 5, and 6, the following relevant points will suffice to summarise the aforegoing (133,135,136,137,138,139,140,141):

- In depressed patients up to a 50% reduction in effectivity has been reported for a wide variety of immunological responses. Immune suppression has been shown by more than 40 independent studies. Some areas of controversy do, however, remain but it should be stressed that a reduced response does not necessarily implicate a decreased activation state.
- There are indications that, despite the immune suppression generally associated with depression, a simultaneous state of immune activation exists. This is not uncommon in a number of medical conditions.

- Many neuroendocrinological factors are involved in the interface between the immune alteration of depression and the altered state of mind, but the two main stress axes, i.e., the HPA-axis and SAM-axis would seem to play pivotal roles. Both axes are known to influence the immune system (see chapters 3 and 5) and are accepted to be disturbed in depression (see chapters 4 and 5).
- Abnormalities in the HPA-axis, and probably the SAM-axis too, are at least partially , related to receptor responsiveness at the feedback level of the hippocampus, the hypothalamus and the pituitary.
- Chronic anti-depressive treatment may not only alleviate the depression but may also normalise the immune status.
- At a cellular level prostaglandins, especially that of the E series, form a strong link between immune and mood alterations. The pervasive function of prostaglandins in immune regulation is well established and evidence is starting to appear which points towards increased levels of PGE1 and PGE2 in depression. The more mechanistic details are touched upon in later chapters. This inference of membrane phospholipid involvement is touched upon elsewhere in this chapter.
- Immunological derived cytokines, known to have a major influence on both the immune system and the behavioural functions, would appear to be the major communicating messengers in the interface. They influence prostaglandin synthesis and are in turn influenced by prostaglandin activity.
- The macrophage hypothesis of depression further implicates a role for cytokines as intermediatory agents.
- There may be a difference between the immune status of clinical (suppressed) and subclinical (enhanced) depression. This would correspond to the differences in immune function induced by mild, acute stress *versus* chronic or uncontrollable stress (see chapter 5).
- Immune alterations of depression may not be specific correlates of the disturbance, but may be shared by other disturbances – both psychological and physical.

2.5.7 Immune involvement in anxiety and anxiety disorders

There is no doubt that a strong link exists between the immune system on the one hand and anxiety and anxiety disorders on the other. It is more than likely that a direct cause-

and-effect relationship exist. A host of evidence to this effect can be found in the literature and is urgently awaiting someone with the experience and initiative to decipher the bidirectional interaction. The link between central monoamine activity and anxiety, as well as anxiety disorders, is relatively well investigated and is discussed in a fair amount of detail in the next chapter. The link between the central neurotransmitters, especially the monoamine neurotransmitters such as noradrenaline, on the one hand, and cytokines on the other, is also becoming clear and seems to be a major focus of contemporary psychophysiological research (142). Evidence exists that immune cell-derived interleukin-1 and tumour necrosis factor-alpha are instrumental in the provocation of both an anxiogenic response and in sickness behaviour. It is likely that these cytokines may mediate their behavioural effects, not only by a modulating influence on hypothalamic neurotransmitter activity, but also by affecting extrahypothalamic neurochemical functioning. (143). Evidence further exists that the central and peripheral benzodiazepine receptors may form a network which in turn may influence the immune system – partially through modulation of the effect of the two main stress axes on the immune system (144). One of the few recent studies that examined the psychoimmunological link with proper consideration of the psychological aspects is that of Borella *et al, 1999* (145). In this study, which dealt with the psychoimmunological link as seen in anxiety, other emotional factors were also taken into consideration and psychological testing included a self-reported measure of emotional stability (BFQ-ES scale), a neuroticism scale (Eysenck personality inventory) and a trait anxiety scale (STAI). The results showed general emotional stability and stable personality traits to counteract the negative effects of transient environment-induced anxiety on the immune system. These results not only explain some of the contradictions of other less well-planned research, but also augurs well for the ability to endure stressful situations without negative physical and psychological side-effects. The reported difference in the immunological response between persons with high trait anxiety and those with high state anxiety (145) has been confirmed by a number of publications that appeared over the last couple of months and some even managed to find a parallel with activation of the noradrenergic axis.

2.5.8 Immune involvement in somatoform disorders

The definition of somatoform disorders, according to the DSM-IV, is the presence of physical symptoms that suggest a general medical condition and are not fully explained by a medical condition, the direct effects of a substance, or by another mental disorder. In contrast to factitious disorders and malingering the physical symptoms are not intentional produced or feigned (146). The prerequisite of *not fully explained by a medical condition* renders these conditions problematic and many patients with real physical problems must have been diagnosed as suffering from a somatoform disorder due to the inability of medical practitioners to identify an existing disease. The reverse is, however, also true and many individuals suffering from somatoform disorders are still being treated for physical conditions.

Over the years various diagnoses have replaced each other for conditions where vague clusters of symptoms were diagnosed as whatever might have been the fashionable syndrome of the day. It is noticeable that most of these syndromes are described as containing an immunological component. Recent *epidemics* considered by some to represent somatoform disorders, rather than general medical conditions, include the chronic fatigue syndrome or yuppie flue, and systemic candidiasis. The so-called systemic candidiasis, thus referred to, represents the relatively mild syndrome of symptoms diagnosed in the general non-hospitalised population as opposed to the life-threatening real systemic candidiasis seen in patients in intensive care units. A manuscript by Panzer and Viljoen, 2001 (147), in which the similarities between some fashionable medical conditions and the somatoform disorders are described, recently appeared in *The South African Journal of Medicine*.

The fact that somatization often involves immunological alterations is easy to understand if one accepts the process to be a consequence of stress, and in view of the effects of emotional stress on the immune system. The following quote from a publication by Ford, 1997, (148) somehow says it all:

The history of "nondisease" dates back, at least 4000 years, to early descriptions of hysteria. More recently somatization became a part of the official diagnostic

nomenclature by creation of the DSM III category, "somatoform disorders." Somatization can serve as a rationalization for psychosocial problems or as a coping mechanism, and for some people, becomes a way of life. One variation of somatization can be the "fashionable diagnosis", for example, fibromyalgia, multiple chemical sensitivities, dysautonomia, and, in the past, "reactive hypoglycemia". These disorders are phenomenologically related to environmental or occupational syndromes and mass psychogenic illness. Fashionable illnesses are characterized by (i) vague, subjective multisystem complaints, (ii) a lack of objective laboratory findings, (iii) quasi-scientific explanations, (iv) overlap from one fashionable diagnosis to another, (v) symptoms consistent with depression or anxiety or both, (vi) denial of psychosocial distress or attribution of it to the illness. Fashionable diagnoses represent a heterogeneous collection of physical diseases, somatization, and anxiety or depression. They are final common symptomatic pathways for a variety of influences including environmental factors, intrapersonal distress and solutions to social problems. A fashionable diagnosis allows psychosocial distress to be comfortably hidden from both the patient and the physician, but premature labeling can also mask significant physical disease. Hysteria remains alive and well and one contemporary hiding place is fashionable illness.

[Ford, 1997 (148)]

2.5.9 Immune involvement in factitious disorders

As factitious disorders are intentionally produced or feigned in order to assume the sick role it approaches a personality trait or need and would therefore not be discussed here. It can, however, often be a product of earlier stressful experiences and this would explain an immunological involvement. (See immunology and early experiences later on in this chapter).

2.5.10 Immune involvement in dissociative experiences and dissociative disorders

The effect of stress on the immune system,, as well as the effect of the immune system on the major stress axes, are indisputable. Some of the immunological effects were discussed earlier in this chapter and the mechanisms are discussed in Chapters 4, 5 and 6. Dissociative disorders such as dissociative amnesia, dissociative fugue, the dissociative identity disorder and the dissociative depersonalisation disorder are generally preceded

by either recent or early traumatic or stressful life events (149). It is thus conceivable that the immune system can be instrumental in the development and progression of such disorders and that these stressful conditions will be accompanied by immune disturbances. The possibility that certain immune activities may also cause dissociation or dissociative disorders is highly feasible if the effect of certain cytokines on the brain and behaviour are taken into consideration. The effects of the immune system on behaviour will be discussed in Chapter 6. The fact that the necessary examples of the stress-immune interactions are discussed elsewhere in this writing obviates the need to deal with such bidirectional interactions in this section. One case does, however, warrant mentioning here, i.e., an interesting example of the psychoimmunological interaction in which a patient with dissociative identity disorder presented with allergic symptoms in certain, but not in all of the personalities (150).

2.5.11 Immune involvement in sexual and gender identity disorders

Some of the hypotheses, that consider the development of homosexuality and certain paraphilias to be a result of intra-uterine development, propose factors such as maternal stress and immunological activity as contributors to the altered sex orientation (151). The ways in which the foetus is influenced by maternal stress and by maternal immunological activity are discussed in a separate section towards the end of this chapter.

2.5.12 Immune involvement in eating disturbances and eating disorders

Anorexia nervosa and bulimia nervosa are generally seen as psychological disorders but are always accompanied by somatic symptoms. The endocrine disorders which result from the undernourishment leads to dysfunctioning of several neurotransmitter systems, including the serotonergic and dopaminergic systems. It has also been suggested that disorders in serotonin and dopamine metabolism may contribute to the development of the eating disorders. These systems have immunological effects of their own and as such makes it very difficult to assess the role of the immune system in the eating disorders. It is known that the immune system, by way of pro-inflammatory cytokines such as tumour necrosis factor-alpha, interleukin-6 and interleukin-1 has a prominent role in the pathogenesis of the anorexia and cachexia of chronic diseases and in the appetite disturbances of diseases such as cancer where the treatment involves the administration

of the pro-inflammatory cytokines (152,153). Whether a primary cytokine disturbance can be implicated in the aetiology of the majority of patients with anorexia nervosa or bulemia nervosa is not clear. What is, however, patently clear is that the immune system can influence the eating behaviour. The immunologically-induced cachectic response of animals immune-stimulated by vaccination is a good example of appetite suppression by immune activity (154). Solid evidence for the effect, as well as a description of the immune mechanisms through which the appetite suppressive effects are being mediated can be found in a recent review (155). The article explains why sick animals don't eat, i.e., the way the immune system interacts with the central nervous system to diminish the motivation to eat and describes the role of the various immune cell-derived cytokines in this phenomenon. It is further known that malnutrition in itself can lead to a suppression of the immune system and that a decrease in appetite is one of the major characteristics of infection. This infection-induced anorexia is considered adaptational, in addition to other factors such as fever (once again a cytokine-mediated effect), that facilitates the defense against invading pathogens (156). A relevant manuscript (**Viljoen and Panzer, 2002**) has been accepted for publication and would be included in the list of references when published.

Other immunological mechanisms may perhaps be implicated in addition to the cytokine-induced effect. There are, for example, indications that auto-antibodies, i.e., anti-dopamine and anti-serotonin antibodies may play a role in the eating disorders (157). Should this type of immune disturbance indeed be a primary cause in some of the eating disorders, certain eating disorders could very well be seen as yet another group of disorders designated to be of autoimmunological origin.

Several other indications are available that give substance to the possibility of a bidirectional influence between the eating disorders and the immune system – none of them disclaiming the role of the psychosocial influence. Of interest is the fact that the influence of immune-derived humoral substances on appetite was noticed long before the majority of cytokines where correctly named. For instance, tumour necrosis factor, a cytokine with various immunological and non-immunological functions, was previously known as cachectin, due to its association with physical waisting.

In summary one can probably say that

- there is no doubt about the immunosuppressive effect of the eating disorders
- a number of cytokines are known to cause appetite suppression
- the immune system, by way of cytokine-release, may contribute to the persistence of anorexia nervosa symptoms
- immunological-induced central neurotransmitter abnormalities can occur which can exacerbate both the eating and the immune disturbance.

However, we are not in possession of absolute proof that immune alterations can primarily underlie eating disturbances – except in the development of autoantibodies. It would, perhaps, make more sense to accept both the disturbed eating behaviour and the immune alterations to be secondary to the effects of the neuroendocrinological activation found in the general non-specific stress response. It speaks for itself that such neuroendocrine activity could, at the very least, partially result from the impact of psychological and psychosocial factors.

2.5.13 Immune involvement in sleep disturbances and sleep disorders

It is generally known that a number of cytokines can change sleep patterns (141). The effect on sleep patterns also forms part of the cytokine-induced sickness-behaviour seen in conditions of infections. The excessive need to sleep during periods of infection-induced immunological activity is said to be a function of cytokine production and a functional behavioural alteration to aid in fighting the infection and recovery. Sickness-behaviour is discussed elsewhere in the thesis.

The sleep disorder most commonly associated with alterations in the immune system is narcolepsy. Narcolepsy, a disorder characterised by excessive daytime drowsiness, cataplexy and sleep paralysis with hypnogogic symptoms may at times also be accompanied by hallucinations. A very interesting link was shown between the hallucinations of narcolepsy and genetic immune defects. Hallucinations are said to be found only in patients who carry one or both of the DR2 and DQW1 HLA alleles. The presence of at least one of these alleles would thus appear to be critical, but not necessary

sufficient, for the development of narcolepsy (158,159,160). An interesting phenomenon which links it to the immune disturbances of other psychiatric disturbances is the fact that inflammation seems to be a prerequisite for the expression of any significant degree of expression of the central nervous system HLA molecules (158,159,160). It is thus again possible that cytokines may be involved in the development and progression of narcolepsy. The link between this immunological prerequisite and the neurological abnormality associated with narcolepsy is still not completely clear and this provides us with wonderfully exciting research opportunities.

2.5.14 Immune involvement in impulse-control disturbances and impulse-control disorders.

A number of publications points towards a possible involvement of the immune system in impulse control disorders such as kleptomania, pyromania and obsessive gambling (161,162). Once again the role of cytokines in the underlying neuroimmunomodulation is implicated.

2.5.15 Immune involvement in adjustment disorders

This group of disorders that include, by definition, conditions of development of emotional or behavioural symptoms in response to identifiable stressors would by necessity show some form of immunological alteration.

2.5.16 Immune involvement in personality traits and disorders, and the impact of personality on immunocompetence

The validity of a causal link between personality and disease development and progression is strangely enough still strongly debated. Despite strong scientific evidence to support the existence of such an association, prominent personalities in the medical field still consider the proposed effect of mental state and disposition as mere folklore (163).

Various associations have been reported between personality and the vulnerability to disease including

- The existence of a self-healing personality (164).
- The existence of a disease-prone personality (165).
- Type A personality and the proness to coronary and other disease (163).
- The so-called Type C personality, or rather the Type C aggregate of characteristics or proclivities said to be associated with the development and progression of cancer (166,167,168,169).

In describing a link between personality and disease some consensus should be reached as to the meaning of the term personality and to the specific aspects of personality proposed to have a bearing on vulnerability to disease. In this context it would be necessary to bridge the gap between the views of personality psychologists and that of health psychologists. Several attempts to this effect have been made – each resulting in its own contribution to the field. Notable is the fact that various groups seem, almost without exception, to identify different personality traits as key factors or as health determinants. McClelland, Alexander and Mark, 1982 (170) for instance, from what appears to be a psychoneuroimmunological point of view, define the motivational processes involved in the need states for power and affiliation, in combination with the environmental restrictions imposed upon fulfillment of such needs, as the key determinants of health. Hardy, 1988 & 1985 (171,172), on the other hand, sees emotions and affect as of great importance, with high hostility as the major risk trait. From a cognitive perspective Scheier and Carver, 1985 (173) define dispositional optimism as the major personality trait for health, while Bandura , 1985 (174), from a social learning point of view, proclaims a sense of self-efficacy as the major positive social determinant of health. Eysenck, 1988 (175), on the other hand, approaches the link from a far more biological point of view. An interesting link between neuroticism and wellbeing has also recently been described and tested as part of a study on a stress model (176) where neuroticism was shown to have a negative effect on health. Several other personality traits, not to be discussed here, have been investigated for a possible link with disease-proneness.

Three major models of explanation for the link between personality and disease proness exist, that according to Suls and Rittenhouse, 1990 (177), are potentially applicable across personality dispositions. These models are:

- The personality-induced hyperreactivity model

This model describes the disease-prone personality as one that appraises events as more stressfull than warranted. Such perceptions will then lead to excessive activation of the non-specific stress response, including that of the two major stress axes. In view of the work discussed in subsequent chapters it is easy to understand how this may lead to immunological and other physical disorders.

- The constitutional predisposition model

This model posits the personality dispositions associated with illness risk to be simply markers of inborn physical weakness that, in turn, predisposes to disease susceptiblity. In other words, both personality and physical illness are secondary to inborn physical weakness. This can really be seen as an erroneous oversimplification – especially when taking into consideration the effects of early life experiences on the neural structures involved in behaviour.

- Personality as precipitator of dangerous behaviour

This model proposes that personality traits may carry greater illness risks (dangerous behaviours) by exposing the individual to riskier circumstances. This idea was recently well exploited by the popular media – especially after the death of John Kennedy (junior).

An in depth discussion of the merits of these models is beyond the scope of this writing, but it is obvious that these models are not at all mutually exclusive and that they could all three, with some adaptations, be usefull for the development of a psychoneuroimmunological model of the personality/disease vulnerability link.

The discussion this far focussed mainly on the relationship between personality traits and disease proness. It is, however, self-evident how the three major models of the linkage could be extrapolated to the development of a testable hypothesis on the link between personality disorders and immune-related disease vulnerability.

Publicatons are starting to appear on a link between personality disorders and immune-derived cytokines like the interferons (178). With cytokines presently seen as the major

mediators between the immune system and neurobehavioural processes, one could certainly expect more of this type of studies to emerge.

2.5.17 Immune involvement in traits and in disorders classified by the DSM-IV as conditions that may be a focus of clinical attention

Many of the conditions in this category are again stress-related which would already implicate an alteration in the immune functioning. Several of the conditions have indeed been researched for their stress effect on the immune system and a number of them were referred to in the paragraphs dealing with the psychoimmunological link in conditions of stress. Although cause-and-effect should be approach with caution, the bidirectional psychoimmunological influence does not allow one to rule out the possibility that immune-derived cytokines may be instrumental or contributory to the development or persistence of some of the behaviour problems of this type.

2.6 Early life experiences and psychoimmunology

The preceding part of this chapter showed the pervasiveness of the interaction between the behavioural and the immunological functions. The question now remains whether the process starts in early life, i.e., whether the mother's behaviour can influence the immune system of the foetus. In addition one should also ask whether the immune status of the mother could influence the behaviour of the foetus. Perhaps of greater importance, should such events take place, is whether the effects are transient or whether they spill over into the adult life of the offspring. The practical implications of both influences, should they last into adult life, would be far reaching. Modification of the foetal immune system by maternal behaviour could, if this does indeed happen, predispose the offspring to infectious or malignant diseases if the effect on the immune system is of a suppressive nature. Should the effect be immuno-enhancing the offspring could be predisposed to the development of autoimmune disorders or chronic inflammatory disease in later life. In addition, the possibility of maternal immune activity having a prolonged influence on the brain and on the future behavioural disposition of the child is equally daunting. Such an effect would then predispose the offspring to behavioural problems and even to mental disorders. The possibility of stress or immunological activity, during neonatal to

adolescent life, having an influence on the future behavioural characteristics and immunocompetence is equally important as this period can still be seen as one of high cerebral and immune system vulnerability to environmental factors.

Most experiments testing the hypothesis that maternal behavioural and immunological characteristics can have major effects on the immune system and future behaviour of the offspring were conducted, either on experimental animals or are based on observations of humans. In the majority of animal experiments, where the mothers were stressed during different periods of the gestational period, high anxiety behaviours were found in the offspring. The differences between the offspring from stressed mothers and the control groups were generally carried over into adult life (179,180,181). As would be seen in subsequent chapters these changes would necessarily have an impact on the immunological characteristics. Direct changes in immune responsiveness have, however, also been reported in the offspring of mothers stressed during the gestational period. Maternal stress would appear to have different effects on humoral than on cellular immunity, with stimulation of the antibody responses and inhibition of the lymphocyte responses (182,183). (This information is important in view of the differential effect of stress on B-cell and T-cell associated cytokines and the difference in their cerebral/ behavioural effects. These aspects are to be discussed at various points throughout the rest of the thesis.) In humans and non-human primates the assumed effects have further been extrapolated from the results of therapeutic and experimental administration of stress hormones or products of the stress response to the mother. These include substances like glucocorticoids (administered to enhance pulmonary maturity), ACTH and interleukins (183,184,185). Results, whether on animals or humans, indicate unequivocally that maternal stress may have a relatively prolonged effect on the immune status of the offspring and that these effects are generally mediated through changes in the structure and functioning of the neurohormonal stress systems of the foetus. The question of whether maternal immunological activity can influence the behaviour of the foetus and by doing so its future stress vulnerability and predisposition to mental disturbances is partially answered elsewhere in this thesis. One of the indications that it may very well do so is the increase reported in the frequency of schizophrenia after major endemic or epidemic infectious conditions (mentioned earlier). Another such indication is

the fact that immunological activity can act as a stressor, and in so-doing, activate the neurohormonal stress response. This, in turn, would lead to predisposition to behavioural alterations. The phenomenon of immune activation becoming a stressor is discussed in later chapters.

In addition to the *in utero* effects, stress during the neonatal and early childhood periods has also been shown to change the immune responsiveness, as well as the behaviour of the offspring. The general result of stress during the neonatal period would appear to be subnormal affiliative behaviour and aggressiveness in adult life (186,187), although other behavoural tendencies were also reported. Once again most of the effects would appear to be linked to changes in the structure and function of the two main stress systems and it is conceivable that such changes would be accompanied by immune alterations. Examples of the influence of separation stress on the immune system of neonatal animals were shown in Table 2.2 in the section that dealt with the effects of stress on animals. The results in Table 2.2 indicated fairly uniformly that early separation exerts a negative influence on the immune system. This, however, is a subject that warrants more than superficial conclusions and many variables should be taken into consideration. The effects of early rearing experiences and social interactions on the immune function in non-human primates, many of them extrapolatable to humans, can be found in an excellent writing by Worlein and Laudenslager, 2001 (188). In it they discuss the validity of non-human primates as models, the immunological effects of variations in maternal rearing, nursery rearing, disruption of the mother-infant bond, disruption of bonds in peer-reared infants, the long-term effects of social separation, disease risks and early rearing effects, as well as the effects of social interaction on immune function in juvenile and adults. It is shown that stressful early experiences not only predispose to infectious complications, but also increase the vulnerability to immunodeficiency virusses, and pathogen inoculation-induced lymphopenia and leukopenia. It is also shown that early experiences can have long-term effects on both the behavioural and the immunological status and that the common intermediatory denominators in both processes are the stress-induced neurohormonal factors – the most important probably those of the two main stress axes (188). One interesting research finding in humans that warrants mentioning is the effect of breast feeding on stress vulnerability and immunity. It would appear that

glucocorticosteroids, transferred to the neonate by means of breast feeding, could exert the same negative feedback on the child's hippocampus-HPA system as the baby's own corticosteroids, and as such lead to lower cortisol production by the neonate or infant (189). This would, in fact, prime him or her to lower base-line HPA-axis activity and, as reported by Catalani *et al,* 1993 (189), may lead to better cognitive performance.

In conclusion, there can be no doubt that *in utero*, as well as neonatal exposure to stress and immunological events can have long-term effects on the future health of the offspring. The final mechanistic details are still relative elusive and inter-individual differences make general assumptions rather dangerous. However, the basis of the behavioural-immunological interaction in foetal life, neonatal life and childhood would appear largely to be a function of alterations in the stress-axes – especially the CRH/HPA-axis. This will be discussed in more detail in Chapter 7 and the central role of CRH in the stress and immune respons in Chapter 5.

2.7 The psychoimmunological interaction and cerebral laterality

It is fairly well known that many neurohormonal as well as structural differences exist between the brains of left handed (right hemisphere dominance) and right handed (left hemisphere dominance) individuals. It is now becoming clear that the hemispheric dominance also extents to the immune system. This is clear from observations that

- Left-sided cortical lesions in mice suppress lymphocyte responsiveness, while right-handed lesions have either no effect or are immuno-enhancing (190,191).
- Left-sided brain tumours in humans result in *in vitro* suppression of lymphocyte responsiveness to mitogens, but no effect is seen with right-sided tumours (192).
- In certain strains of mice, females, but not males, with left paw preference, i.e., right hemispheric dominance, were shown to exhibit a stronger non-specific lymphocyte response than right paw preference animals (193).
- Some, but not all, reports point towards a higher incidence of autoimmune diseases in left-handers (194).

The mechanisms involved in the above differences are not yet clear but indications are one again pointing towards handedness-associated differences in the two main stress axes. Whether this is accompanied by changes in stress-vulnerablity and other behavioural differences one can only speculate on, but it certainly offers an interesting field for future research. An interesting point that may perhaps have a bearing is the fact that the immunologically-induced stress response corresponds, neurohormonally, very much to that of the psychologically-induced stress response, except for its effects on the central dopaminergic systems. This will be discussed in Chapter 6.

2.8 The psychoimmunological interaction in overview

The immune system was initially seen as a fairly autonomous system thought to function relatively independently of other systems. In this capacity its functions centered around the defense against pathogen invasion and against neoplastic growth, while maintaining self-tolerance. This model of the immune system is sometimes referred to as the defense model (195). Gradually, however, it became clear that other factors such as the endocrine system can influence immunoreactivity and that the immune system may have a regulatory role in the functioning of other systems. The influence of the psychological disposition on health, long since noticed by the general population, only gained scientific recognition over the last couple of decades. In fact, this interaction, of which some of the mechanisms are only now starting to be understood, had already been accepted by early civilisations. Ancient Greek medicine for instance recognised the cause-and-effect association between the state of mind and the resistance of the body against disease (195).

The identification of immunological cell surface molecules on neural structures and the neuroendocrine receptors on immune cells gave rise to the Darwinian approach of the psychoimmune interaction (196). The Darwinian view of the psychoimmune relationship states that the immune system and the neural system, somewhere in the distant phylogeny, used to be one and the same system. This approach would, in theory, explain the similarities in receptor expression, adhesion molecules and secretory ability between immunological and brain cells. It could, from this point of view, be argued that the immune-associated receptors on brain cells and the neural receptors and secretions of

immune cells are actually of a vestigial nature, and therefore of no functional significance. The common origin of the immune and neurological systems, as postulated by the Darwinian approach, appears, from available evidence, highly feasible. However, the assumption of the vestigial nature of the shared structures does not concur with clinical and research observations, and it is more likely that they form part of a regulatory feedback mechanism between the two systems. Proof for this statement can be derived from the multi-directional influence between the psychological and immunological activity, as shown in this chapter, and from the bidirectional interactions described in subsequent chapters.

The outcome of psychoimmunological interactions is without doubt not merely a function of the effect of the immune system on the psychological disposition and *vice versa.* Almost all other physiological systems, as well as environmental factors can influence the relationship. A more lateral approach is seen in the biopsychosocial model of the psychoimmunological interaction that gives recognition to this effect. The model is depicted in Figure 2.2.

The biopsychosocial model of the psychoimmune relationship, as depicted in Figure 2.2 was developed in an attempt to facilitate the organisation and understanding of the evidence supporting the relationship between stress and immune alterations. The model depicts the way in which social, psychosocial and biological aspects relate to the immune dysfunction that follows upon adverse life events. The historical importance of this model of psychoimmunological interaction renders it necessary to quote the authors directly so not as to misconstrue their intentions:

> *This model predicts that certain combinations of stressors and buffers in the social environment, coupled with the personal characteristics of an individual, determine the way in which the individual perceives the stressor and subsequently adapts psychologically. For example, personal characteristics, such as age and health, and psychological and environmental factors, such as social support and employment status, converge with the individuals personality to predict the persons coping and the psychological adaptation to*

stress. Psychological maladaptive behaviour, as measured by symptoms of imsomnia, anxiety, or depression, is then postulated to mediate changes in neuroendocrine and autonomic efferent pathways from the brain to alter immune function. Such decrements in immunological competence are purported to produce and increase disease susceptibility and changes in health outcome. In addition, the individuals perception of the stressor may directly result in sleep disturbances or alcohol abuse, which may produce direct effects on the immune system leading to compromised health. Because health changes in and of themselves may be psychological stressful, it is possible that a bidirectional pathway exists between stress and illness. For example, health changes can actually change the social environment (e.g., levels of social support) and may have independent effects on such variable biological variables as neuroendocrine and immune function.

Irwin and Strausbaugh, 1991 (198)

Later models in a series of consecutive models usually have the advantage of drawing on more advanced scientific knowledge than previous models. The biopsychosocial model, although of major developmental importance, is no exception. The model was designed at a stage when very few longitudinal studies had been conducted on the long-term effects of stress, when stress was predominantly seen as a negative influence, and when most of the physio-anatomical alterations of stress had not yet been experimentally confirmed. The model was thus largely a theoretical model. It therefore contains a number of misconceptions such as the incorrect assumption of the meaning and placement of the stress concept. Although the value or contribution of the biopsychosocial model should not be dismissed, the time has perhaps come to look at the interaction between body and mind, not only from a wider perspective, but also with a greater understanding of the underlying mechanisms. It is also essential that an interactive model should be developed beyond the prevailing concept of stress merely as a negative condition. The biopsychosocial model, in fact, still errs in its interpretation of the meaning of the word *stress* by seeing it as a stressor. If nothing else, this error should be corrected and the word stress replaced with the term stressor. It is, however, also necessary to reconsider the entry point of the stressor in the model.

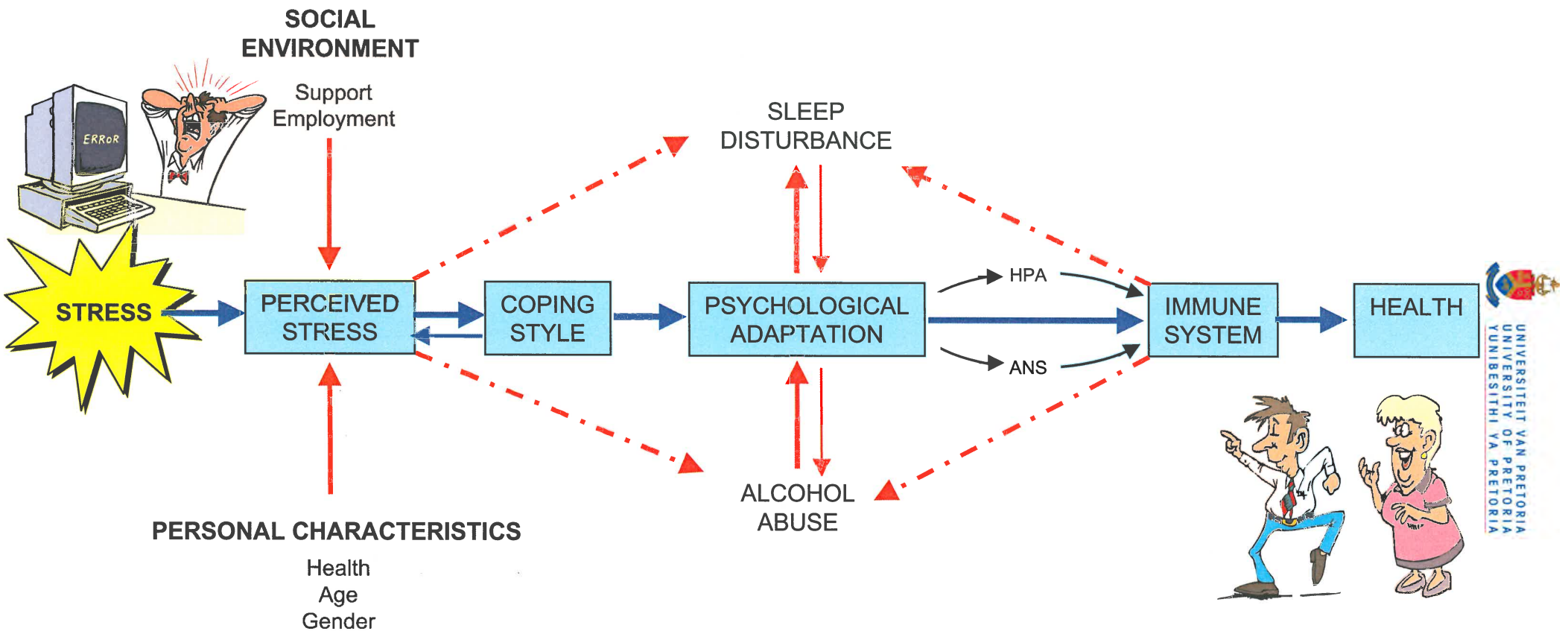

Figure 2.2: Biopsychosocial model of the relationship between stress and health.
(HPA = hypothalamic-pituitary-adrenocortical axis; ANS = autoimmune nervous system.
Adapted from (198))

Adaptation of this model was, however not the aim of this chapter. The purpose of the chapter was to demonstrate the all pervasiveness of the immunological involvement in psychological processes – information not available at the time when the biopsychococial model of psychoimmunology was developed.

This overview provided evidence for the association between the psychological and immunological aspects without in depth discussions on the mechanisms. In an attempt to reduce the volume of the work only selected examples were discussed. Important subjects omitted include the interaction in conditions of cancer and the psychoimmunological therapies. These topics are, however, widely reviewed elsewhere (199,200). In summary, it can be said that this chapter demonstrated the interaction between the psychological and the immunological aspects not only to be a characteristic of a limited number of specific psychological phenomena, as would mistakenly be assumed upon a more superficial scrutiny of the literature, but probably of all psychological conditions. The psychoimmunological interaction can with a fair amount of certainty be concluded to be of a multi-directional nature as can be seen in the mental disturbances which follow upon immune stimulation by infectious and other agents and in the fact that the immune system can be manipulated by processes such as psychological conditioning, placebo, psychological stress and a variety of psychotherapies.

Important questions do, however, remain to be answered in order to better understand the link between the psychological and immunological activity. Some of these questions are asked below and tentatively answered. The rationale for the answers are to be found in the following chapters.

- What comes first; the immune disturbance or the psychological disturbance? In some cases this is answerable, but in others not.
- Could the link not be secondary to medication or other external factors? The answer must surely be yes, that it does occur, but that such events do not negate the existence of a pervasive influence between behaviour and immunity.
- Could the correlation not merely be an epiphenomenological occurence with both disturbances primarily related to neuroendocrine or other functions? An example of

this would be the stress-induced activation of the two main stress axes with their potential immunological and psychological effects? Again the answer is an unequivocal yes to the effects of the neuroendocrine systems as intermediatory factors. Of course structural-functional multidirectional relationships exist between the behavioural, neuroendocrinological and immunological systems – this is the way most human processes work.

- Could the immunological and the mental changes not perhaps form part of a general sickness behaviour or general physical and psychological dyshomeostasis? It could, but the processes are not limited to conditions of dyshomeostasis. In fact, it is merely a reflection of the total integrated control of the body in which the immune system and the neuroendocrine system are the two major regulatory mechanisms.
- Are there common denominators between the immunological alterations of various psychological conditions or are the immune changes specific for specific behavioural patterns and disorders ? This is not clear at the moment but indications are that minor variations are specific within an overall non-specific pattern.
- Are there common denominators or patterns in the immunological patterns associated with psychological phenomena and those associated with medical conditions? It is extremely tempting to answer this in the affirmative – especially where mediators of the inflammatory process are concerned.
- What is the magnitude of the influence of inherited variances in genetics, e.g., in the HLA classes and others? The influence of genetics is indisputable, but indications are that, except in cases of overt genetic abnormalities, positive psychosocial experiences can compensate.
- To what extent can psychosocial influences alter the relevant immunological gene expression? It would appear that both genetic predisposition and adverse psychological experiences are necessary for overt psychoimmunological pathology to develop. Positive psychological influences could therefore act as buffer against expression of a negative genetic predisposition.
- What exactly is the clinical significance of the interaction? Once again, it is simply part of the normal regulatory mechanisms necessary for both physical and psychological development and wellbeing. It is only when either psychosocial or

physical environmental influences impacts negatively on either one that psychological and physiological dyshomeostasis may develop.

The aim of this thesis is to provide a framework for an integrated approach to the mind-body interaction in terms of the two main stress axes. Although a psychoneuroimmunological approach, as an extension of the stress paradigm is adhered to, the mind-body interaction would be understood to involve all aspects of physiological and psychological functioning. The term *mind-body interaction* would, in view of the envisaged endpoint of the work, perhaps already be a contravention of the approach and could perhaps be better defined as *mind-body unity*. The idea of a mind-body unity would concur with my own inclination of seeing the psychoimmunological interaction primarily as a reflection of the unity of mind and body with all aspects influencing and being influenced by all other aspects. Such an approach would be in agreement with a wider understanding of the psychoneuroimmunological approach.

The initial chapter dealt with the historical background and the various approaches to the mind-body interaction. In line with the aim of this thesis the present chapter provided examples to support the notion of a pervasive interaction between the psychological and the immunological aspects without giving mechanistic details. The chapter thus dealt with the psychoimmunological aspects of psychoneuroimmunology. The subsequent three chapters will be confined to the psychoneurological and neuroimmunological aspects, respectively.

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