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PSYCHONEUROIMMUNOLOGY

IN TERMS OF THE TWO MAIN STRESS AXES

Sickness Behaviour as Trigger for the Development of Mental Disorders

by

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SUMMARY

The thesis deals with the mind-body paradox in psychoneuroimmunological context. Psychoneuroimmunology is defined as a post-modern approach to the mind-body connection. It is an extension of the stress paradigm. The thesis therefore concentrates on psychoneuroimmunology in terms of the two major stress axes, i.e., the central noradrenergic/sympatho-adrenomedullary-axis (CNA/SAM-axis) and corticotropin-releasing hormone/hypothalamo-pituitary-adrenocortical-axis (CRH/HPA-axis). The psychoimmunological link is investigated and a pervasive connection is shown between behaviour and immunology, as well as immune disturbances in mental disorders of most categories of the DSM-IV. The psychoneuroimmunological interaction in terms of the two main stress axes is demonstrated by consecutively examining the psychoneurological and neuroimmunological interactions of the CNA/SAM-axis and CRH/HPA-axis. A total interdependence between the psychological, neuroendocrine and immunological functions is shown to exist, not only in adult life, but also during the developmental perinatal period. It is seen that corticotropin-releasing hormone (CRH) constitutes the principle neuropeptide in the regulation of the neurobehavioural stress response and that psychoneuroimmunology in terms of the two main stress axes can be equated to psychoneuroimmunology in terms of CRH. CRH is, in fact, shown to act as central coordinator and integrator of neuroendocrine, immunological, autonomic nervous system, motor and behavioural functions through the pervasive distribution of its cell bodies and projections throughout the central nervous system. The mechanisms through which peripheral events such as infectious, inflammatory and traumatic complications can influence behaviour are subsequently examined and it is seen how peripherally derived cytokines can transfer information to the central nervous system and in this way alter neuroendocrine function and behaviour. The CRH/HPA-axis, and CRH *per se* is, in line with its central regulatory and coordinating role, shown to be a major target for the modulatory actions of cytokines. The thesis is concluded by presenting sickness behaviour as practical example of the psychoneuroimmunological interaction. A hypothesis is presented describing sickness behaviour as adaptational new homeostasis with the potential to develop into mental disorders in those individuals so predispose by genetics and adverse early life experiences. Cross-sensitisation between

cognitive and non-cognitive stressors is seen to exacerbate the potential threat to mental as well as physical health. Once again the CRH/HPA-axis is shown to fulfill a central role in the development and expression of sickness behaviour and in the transition to mental disorders.

Psychoneuroimmunology provides the link between many previously inexplicable connections between mind and body. It explains how negative emotions can induce immune dysregulations with considerable health risks, and how peripheral events such as infections and physical trauma can predispose to short- and long-term behavioural disturbances. Psychoneuroimmunology, in fact, demands a paradigm shift in our approach to the mind-body paradox.

Key words: Psychoneuroimmunology; psychoimmunology; immunology; behaviour; mind-body; central noradrenergic/sympatho-adrenomedullary-axis; corticotropin-releasing hormone/hypothalamic-pituitary-adrenocortical-axis; stress; cytokines; cortisol; pro-inflammatory; sickness behaviour; mental disturbance.

OPSOMMING

Die tesis handel oor die gees-liggaamsparadoks in psigoneuroimmunologiese konteks. Psigoneuroimmunologie word gedefinieer as 'n postmoderne benadering tot die gees-liggaamverwantskap. Dit is 'n uitbreiding op die stresparadigma. Om hierdie rede word daar dus gekonsentreer op psigoneuroimmunologie in terme van die hoof stresasse, dws, die sentrale noradrenerge/simpato-adrenomedullêre-as (SNA/SAM-as) en die kortikotropien-vrystellingshormoon/hipotalamo-adrenokortikale-as (KVH/ HPA-as). Die psigoimmunologiese verband word ondersoek en 'n deurlopende verwantskap tussen gedrag en immunologiese veranderings gevind. Immunologiese versteurings word ook in feitlik al die kategorië van die DSM-IV aangetoon. Die psigoneuroimmunologiese interaksies word bevestig deur agtereenvolgens die psigoneurologiese en die neuroimmunologiese wisselwerkings in terme van die SNA/SAM-as en die KVH/HPA-as te ondersoek. Daar word aangetoon dat 'n totale interafhanklikheid tussen die psigologiese, die neuroendokriene en die immunologiese funksies bestaan - tydens volwassenheid, sowel as gedurende die perinatale ontwikkellingsfases. Daar word gewys dat kortikotropien-vrystellingshormoon (KVH) die belangrikste neuropeptied vir die regulering van die stresresponse is en dat psigoneuroimmunologie in terme van die twee hoof stresasse gesien kan word as psigoneuroimmunologie in terme van KVH. Daar word inderwaarheid bewys dat KVH, as gevolg van die wye verspreiding van KVH selliggame en projeksies in die senuweestelsel, die sentrale koordineerder en integreerder van neuroendokriene, immunologiese, outonome, motor en psigologiese funksies is. Verder word aangetoon hoe perifere sitokien-induserende aktiwiteite, soos infeksies en trauma, die neuroendokriene funksies en gedrag kan beinvloed. Dit word gesien dat die KVH/HPA-as, en in besonder KVH, 'n belangrike sitokienteiken is. Die tesis word saamgevat deur siektegedrag as praktiese voorbeeld van die psigoneuroimmunologiese interaksie uit te beeld. 'n Hipotese van siektegedrag as 'n aanpassingshomeostase met die potensiaal om oorsprong te gee aan psigologiese versteurings, word geformuleer en verdedig. Daar word verder aangetoon dat genetiese disposisie en vroeë lewenservarings die individu kan predisponeer tot die omskakelling van siektegedrag na gedragsversteurings. Dit word ook duidelik dat die potensiaal van siektegedrag om aanleiding te gee tot psigologiese versteurings nie

slegs beinvloed word deur genetika en vroeë lewenservarings nie, maar ook deur kruis-sensitisering tussen kognitiewe en nie-kognitiewe stressors. Die KVH/HPA-as word weereens waargeneem as sentrale determinant in die ontwikkelling en ekspressie van siektegedrag en in die oorskakeling na psigologiese versteurings.

Psigoneuroimmunologie verklaar die verband tussen talle voorheen onverklaarbare assosiasies van liggaam en gees. Dit verduidelik ook hoe negatiewe emosies kan lei tot immuunwanregulering met gevolglike gesondheidsrisiko's, en hoe perifere gebeurtenisse soos infeksies en beserings die individu kan presensitiseer vir die ontwikkelling van kort- sowel as langtermyn gedragsversteurings. Psigoneuroimmunologie vereis inderdaad 'n paradigmaverskuiwing in ons benadering tot die gees-liggaamsparadoks.

Sleutelwoorde: Psigoneuroimmunologie; psigoimmunologie; immunologie; gedrag; gees-liggaam; sentrale noradrenerge/simpato-adrenomedullere-as; kortikotropien-vrystellings hormoon/hipotalamo-pituitere-adrenokortikale-as; stres; sitokiene; kortisol; pro-inflammatories; siektegedrag; gedragsversteuring.

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CHAPTER 1

INTRODUCTION

Approaches To The Mind-Body Paradox And Introduction To Subsequent Chapters

Psychoneuroimmunology introduces the immune system into the psychoneurological equation of the mind-body relationship. The aim of this thesis is to define the mind-body connection in psychoneuroimmunological context in terms of the two main stress axes. It is shown that the mind-body relationship involves more than a two-way street between neuroendocrine function and behaviour and that the immune system is of paramount importance in the information flow. Behaviour is seen as biological response modifier and *vice versa*. A schematic interpretation of the psychoneuroimmunological interaction, in terms of the major stress axes, is developed and presented. The thesis is concluded by a practical example of the relevant psychoneuroimmunological interactions, followed by a hypothesis on the implications of these interactions for mental health. Chapter 1 provides a very brief overview of the major past and present approaches to the mind-body problem, some of them now only of historical interest. This is followed by defining the term psychoneuroimmunology, and a short description of the field and its origin. The chapter is concluded by a lay out of the rest of the thesis.

Introduction

The first three sections of this chapter take a brief look at developments in the mind-body concept over several centuries, without entering into the argument about the merits of the different schools of thought. It is subdivided into:

1.2 Cross-cultural perspectives on the mind-body situatedness

1.3 Current views on the mind-body relationship

Subsequent sections comprise an introduction to psychoneuroimmunology, and explain the organisation of the rest of the thesis. These sections are:

1.4 Introduction to psychoneuroimmunology

1.5 Organisation of subsequent chapters

1.1 Historical perspective on the mind-body paradigm

1.1.1 From philosophy to psychology

The mind-body paradox has been a major problem long before the formal beginning of psychology as an independent science. It is said that speculation about the origin of mental processes is probably as old as the process of thinking (1). The earliest recorded views on the origin of mental processes are those of the ancient Greeks and include the teachings of Heraclitus (6^{th} century BC) who saw the mind as an endless space and Aristotle (4^{th} century BC), who saw the heart as the centre of nervous control and as the seat of the soul (1). This concept of a physical seat or location of the mind had been addressed by many and although the brain is now generally seen as the physical basis of cognitive-emotive processes, persuasions vary with some still resembling the endless space concept of Aristotle. Over time the changing views of the mind-body link, as can be expected, largely reflected the changing physical worlds that surrounded their founders. Examples of this are seen in the views of a) Galen who saw the fluid-filled cavities of the brain as the functionally essential parts – thus reflecting then prevailing technological developments in aqueduct and sewer system construction, b) Kepler, describing the eye as optical instrument, and Willis, recognising that hearing occurs as a result of the ear's transformation of sound – the work of both reflecting the era of mechanics and c) Du Bois-Reymond who explained brain function in terms of chemical and physical principles – an outflow of the discovery of electricity by physicists (1).

Although experimental research into the mind-body relationship is generally said to have started around the 17th century, it actually dates back to the second century AD. One would have expected a certain stepwise increase in our understanding of the mind-body interaction over the ages. This, however, is only partially correct, as progression and regression in the lines of thought seem to alternate. The reason for this can to some extent be ascribed to the lack of communication, not only as a result of physical separation between investigators, but also as a result of non-communication between the various disciplines.

The majority of early mind-body positions in psychology were derived from the field of philosophy. In fact, the mind-body problem is said to be bequeathed to the sciences by philosophy. Although the positions of philosophers, psychologists and others cannot always unequivocally be defined and many questions remain as to their exact viewpoints on the matter, it is reasonable to classify the various positions, at least from a historical point of view, into three main schools of thought. Such a tentative classification, as described by Marx and Cronan-Hillix, 1987 (2), divides the mind-body approaches into dualistic, monistic and compromising:

- The position of dualism is defined as any approach that accepts a basic difference between mind and body and, by implication, a relationship to be explained. It comprises Cartesian interactionism, psychophysical parallelism and occasionalism. Cartesian interactionism, with Descartes (1641) as major exponent, assumes the mind-body association as two separate but interacting processes. The second dualistic approach is psychophysical parallelism. Psychophysical parallelism, as represented by Spinoza (1665), defined the mind-body relationship as two separate, independent, yet perfectly correlated processes. However, other definitions of the term also exist. The third variation on the dualistic position, i.e., occasionalism, assumes the mind-body connection as two separate and independent processes correlated by the intervention of God. Malebranche (1675), represents an early significant exponent of occasionalism. Several variations on the original three dualistic mind-body positions are presently in existence and some will be touched upon in later paragraphs.

- Monism, as opposed to dualism, includes all positions that ignore either mind or body or that subsume both mind and body under the same axiom. Monism, as position on the mind-body connection, includes materialism, subjective idealism and phenomenalism. Materialism, as a monistic viewpoint on the mind-body connection, postulates a single underlying physical reality. This viewpoint dates back to Democritus, 400BC. The second form of monism, i.e., subjective idealism, in contrast, presumes a single underlying mental or spiritual reality. Berkeley (1710), represents an important exponent of this sub-position (2). Phenomenalism, as represented by Hume (1740), proclaimed that neither mind nor body exists, only ideas derived from sense impressions (2). Some of the contemporary variations on monism are discussed later in this writing under *current views of the mind-body relationship*.
- A third group of approaches on the mind-body connection, in addition to dualism and monism, can be seen as the compromises. The two main schools of thought classified under compromises are the double-aspect view as represented by the assumptions of Russell (1915), and epiphenomenalism with Hobbes (1658) as major early exponent. The double-aspect view or dual-aspect theory assumes mind and body to be a function of one underlying reality, while the epiphenomenalistic sub-position sees mind as a non-causal by-product of the body (2).

The above classification provides a degree of order to the different viewpoints on the mind-body dilemma. It does, however, introduce its own problems. One major stumbling block in classifying viewpoints according to the above classification lies in the changing concepts of the definitions on the positions and sub-positions. An example of this is seen in the perception of the dualistic approach of psychophysical parallelism. Psychophysical parallelism, as represented by Spinoza (1665), is generally said to define the mind-body relationship as two separate, independent, yet perfectly correlated processes (2). Some interpretations, however, define psychophysical parallelism by saying, amongst others, that every mental process coincides with a neurophysiological process – without specifying either a causal or non-causal relationship between them (3). The latter renders the whole concept hanging and makes it impossible to differentiate between psychophysical parallelism and monistic sub-positions. It is obvious that a causal

relationship would move psychophysical parallelism beyond the dualistic position. The same confusion exists with regard to Cartesian interactionism. Recent analysis of the work of Descartes suggests that his position might have been misinterpreted for quite a while (4). In an article by Duncan, 2000 (4) the philosophies of Descartes are compared to the modern biophysical model of pain and similarities are pointed out, stressing the fact that the present view of what Descartes said is quite different from what was originally intended. The question is, not unjustifiable so, asked in what respect contemporary theories represent, in philosophical terms, significant advances over that of Descartes. Similar variations in conceptionalisation of viewpoints can be found for both the monistic approach and for the compromises. The double-aspect view, or dual-aspect theory is, for instance, said to have assumed mind and body to be a function of one underlying reality (2), while others define the position's viewpoint as seeing the mind and body as two aspects of the same thing (5). Should mind and body be understood as two aspects of the same then the double-aspect view approaches the reductionistic present day version of materialistic monism. The same dilemma applies to epiphenomenalism. The epiphenomenalistic subposition is said to see mind as a non-causal by-product of the body (2). However, current psychological dictionaries define epiphenomenalism as the view that psychological processes are merely by-products of neurological processes without any influence on the body or on subsequent psychological events (6). The latter definition once again has a strong leaning towards materialistic-monism.

The three positions touched upon in the previous paragraphs are, with some additional comments, summarised below:

Dualism (assumes the existence of a basic difference between mind and body):

- *Cartesian interactionism* (mind and body separate but interacting – debate on whether this definition really concurs with Descartes' intentions).
- *Psychophysical parallelism* (mind and body separate, independent, but correlated. Also defined as every mental process coinciding with a neurological occurrence, a definition, but for the causality, not that far removed from the monistic approach).

- *Occasionalism* (mind and body separate, independent, correlated by the intervention of God – a view still adhere to in certain religious circles).

An easy way to understand the difference between the three types of dualisms is to look at the factors said to mediate the interaction between mind and body: in Cartesian interactionism there is a mutual influence, in psychophysical parallelism mind and body are created to function in unison and in occasionalism the functioning of mind and body are correlated by the influence of God or, as also referred to, by a Skilled Workman.

Monism (an approach which ignores either mind or body or subsumes both under the same rubric):

- *Materialism* (single underlying physical reality to mind and body – the major current perspective, sometimes seen as too reductionistic. Further subdivisions or versions are touched upon later in this chapter).
- *Subjective idealism* (single underlying mental reality to mind and body. Also been referred to as immaterialism or mind-stuff).
- *Phenomenalism* (no mind or body exist – only impressions).
- *Neutral monism (Sometimes seen as compromise. See compromises for dual-aspect).*

Compromises

- *Double-aspect view* (mind and body seen as a function of one underlying reality. In the 17th century version God is seen as the one and only underlying reality. In the 19th century version it is known as dual-aspect monism or neutral monism where mind and body are seen as different aspects of the same "stuff" – different aspects of the same psychophysical process.)
- *Epiphenomenalism* (mind seen as non-causal by-product of body – also defined as mind being a by-product of neurological processes, unable to reflect back onto nervous system - once again moving towards the materialistic monistic approach)

It is interesting to note that every one of the above versions of explanation on the mind-body relationship still has it's following and that most of the current, apparently new approaches are to a certain extent variations on one or more of the above.

1.1.2 Approaches from the schools of psychology

The mind-body problem has to some extent, been addressed by almost all schools of psychology – many of the earlier schools still leaning heavily on arguments from the discipline of philosophy. The latter statement is especially relevant with regard to associationism, a school with its origin firmly rooted in philosophy. Associationism defined the processes of the mind as products of learned associations between smaller elements such as simple ideas and sensations (7,8). Antecedent associational influences from philosophers including Hobbes and Berkeley were mentioned earlier under the heuristic discussion of the major historical positions of philosophy on the mind-body connection. Important exponents of associational psychology include the assumed founder David Hartley (1705-1757), as well as developers such as Thomas Brown (1778-1820), James Mill (1773-1836), John S Mill (1806-1873), Alexander Bain (1818-1903), Hermann Ebbinghaus (1850-1909), Ivan Pavlov (1849-1936), Vladimir M Bekhterev (1857-1927), Edward Thorndike (1874-1949) and Edwin R Guthrie (1886-1959) (9). Several philosophical arguments but no clear point of view on the mind-body problem would appear to be derived from associationism. Edward Thorndike, generally seen as an important exponent of associationism, largely preferred to ignore the problem and made no significant formal statement on the problem The closest one can probably come to a formal statement on the problem is a writing from his student days:

The real absurdity is to settle beforehand what mind or matter can cause without empirical study of the phenomena of the connection between mind and body. No one proves that causation is impossible between heterogeneous orders of being just by saying so in a loud enough voice. And the psychologist who affirms without other reason that because the mind moves the particles of the brain, it must be material, like a pumpkin, has a mind that is enough like a pumpkin to partially justify him.

Joncich, 1968, p139 (10 as quoted in 9).

Structuralism, in an attempt to decipher the modes or structures of associations, analysed consciousness or awareness in terms of its simplest elements (11,12). From the school of structuralism one ought to look at the mind-body positions of, at least, Wilhelm Wundt

(1832-1920) (13) and that of Titchener (1867-1927) (14). Wundt, the founder of structuralism, despite his emphasis on experimentation and his writing of *Principles of Physiological Psychology (1910) (15),* had a great interest in philosophy and his position on the mind-body connection is therefore often classified along the lines of philosophy (13). Having said that, it is necessary to note that some confusion still exists as to his actual place amongst theorists on the problem. Wundt saw mind and body as parallel, but not interacting systems. Wundt has been described by Boring (1950) as dualist, by Blumenthal (1980) and Richards (1980) as identity theorist (as he described himself), with mind and body as two aspects of the same underlying identity, and by Hoorn and Verhave (1980) as parallelist, an opinion based on the nature of his work (13). Titchener, another major exponent of structuralism is, although of British origin, considered to be the founder of the American brand of structuralism (14). With minor differences Titchener's position on the mind-body connection is in agreement with that of Wundt in that both concurred mental and physical events as running along parallel courses (16). Their opinions on whether the mind-body relationship is monistic or dualistic may, however, have differed. Indications that Titchener's position should be seen as monistic, as opposed to a more dualistic leaning on the side of Wundt, can be derived from the following quotation:

> *The metaphysics to which Science points us is rather a metaphysics in which both matter and spirit disappear to make way for the unitary concept of experience.*
>
> *Titchener, 1899 (17 as quoted in 16).*

Whether this implied monism reflects an idealistic theory, where consciousness is the only reality, or an identity theory, where the nature of the reality (mental or physical) is not specified, is not clear and of little importance. It is at this point perhaps interesting to note Titchener's views on the meaning of mind and on that of consciousness. He defined mind as the sum total of a persons experiences from birth to death as opposed to consciousness that he defined as the sum total of experiences at any given time (14). This view would even today make sense.

In the school of functionalism, as in most other schools of psychology, opinions about and interest in the mind-body association varied widely. In contrast to structuralism, functionalism focussed on the functional contributions of larger psychological units of behaviour as a means of adaptation to the environment (18,19). In trying to understand the general trend in the mind-body approach of functionalism, it is relevant to remember that scientists such as Sir Francis Galton (1822-1911) and Charles Darwin (1809-1882) were among the antecedent influences on functional psychology – a fact that may very well have been a major determinant in their mind-body approaches. The school of functionalism shows a typical progression-regression pattern in the development of the understanding of the mind-body connection. Major advances are derived from the work of William James (1842-1910) (20). Important accomplishments by William James, pertaining to the mind-body connection, include the James-Lange theory of emotion, his work on the connection between consciousness and neurons and his point of view that consciousness cannot be considered as apart from the body. James therefore can be classified with more recent psychologists who see the mind-body connection as one of interaction, or perhaps rather of unity. One further aspect of his work that should be mentioned in relation to the mind-body interaction is that of adaptation. Not only did he believe in physical adaptation to the environment but, in addition, brought in instinct, memory, attention, habit, choice, as well as the relationship between these different functions (20). This, at first impression, places him right there with many modern day neuroscientists. His later conclusions are, however, not that simple and will be returned to later in this text. Most functionalists, other than William James, contributed very little to the study of the mind-body problem. In fact, developments during this period was in a constant state of fluctuation and positions varied from parallelism to the feeling that psychologists don't need to concern themselves with metaphysical problems, to simply assuming the psychophysical interaction without further questioning (21). The latter approach especially applied to a group of functionalists that included Harvey Carr (1873-1954) and several others, who did not see the mind-body connection as a problem and simply accepted the psychophysical integration (21). This approach is also seen in many of the cross-cultural and post-modernistic perspectives to be discussed later.

Behaviourism, best known for its stimulus-response approach, comprises two major approaches to the mind-body link. Empirical or methodological behaviourism that had very little interest in the mind and focussed only on observable behaviour, and radical or metaphysical behaviourism that denied the existence of the mind (22, 23). The latter form of behaviourism can be seen as a form of physical monism. The behaviourist school of psychology (24) was, in its quest to define the mind-body relationship, perhaps most severely handicapped by the concept of *consciousness* and, to a lesser extent, the concept of *mind*. Many behaviourist declined to investigate the meaning of *consciousness* or *mind* and would not attach much importance to either of these issues. Typical behaviouristic remarks include:

The plans that I most favour for psychology lead practically to the ignoring of consciousness in the sense that that term is used by psychologists today. I have virtually denied that this realm of psycics is open to experimental investigation. I don't wish to go further into the problem at present because it leads inevitably over into metaphysics.

Watson, 1913 (25 as quoted in 24).

Consciousness is a purely personal experience and has no scientific value or validity unless it is expressed in some form of behaviour.

Weiss, 1917 (26 as quoted in 24).

By 1924 Watson concluded that the existence of consciousness is totally improvable and that those who wants to introduce it either as an epiphenomenon or an active form into the physical or chemical body is motivated to do so by spiritual or vitalistic notions (24).

Other extreme positions from the school of behaviourism include the tendency to completely reduce the mind to physiological function, the denial of the existence of consciousness, the argument against a connection between body and mind based on the assumption that the interaction between non-physical events with physical events violates the principle of the conservation of energy, and radical physical monism postulating mental as a mere description of the mode of action of physical events with no room for

the existence of an independent consciousness (24). In summary it can be said that several positions appealed to individual behaviourists, most preferring to take a strong position on the dilemma without a need to study either mind or consciousness.

Gestalt psychology, with founder exponents like the psychologists Max Wertheimer (1880-1943), Kurt Koffka (1886-1941) and Wolfgang Kohler (1887-1967), has often been said to try and sidestep the issue of mind-body connection (27). The validity of such a statement is, however, questionable. In line with the primary postulate of gestalt psychology that states the whole to be primary to and different from the parts, gestalt psychology implies mind and body as a functional unity - which minimizes rather than evades the problem. This assumed position of mind-body as an integrated unit has on occasion been critisized as in contradiction to what is seen as their particular understanding of the principle of isomorphism (the concept that each psychological process is accompanied by a neurophysiological process) - arguing that their position rather leans towards dualism (29). Whether meaningful or not, the latter approach to the gestalt position was in turn criticised by the view that isomorphism was not intended as an explanation of the mind-body relationship. To quote Prentice, 1959 (29):

Let me say once and for all that the concept of isomorphism is not an attempt to solve the mind-body problem in its usual metaphysical form. It takes no stand whatsoever on whether mind is more or less real than matter. Questions of reality and existence are not raised at all. Mind and body are dealt with as two natural phenomena whose interrelations we are trying to understand. It comes nearest perhaps to what has sometimes been called the double–aspect theory, the view that cortical events and phenomenal facts are merely two ways of looking at the same natural phenomenon, two faces of the same coin. Prentice, 1959 (29)

Despite the arguments of Prentice many are still of the opinion that isomorphism does in fact offer a specific solution to the mind-body body problem – a way of integrating the mind with the rest of the world (30). Whatever the finer points of argument, it can unequivocally be said that the gestalt position on the mind-body situatedness is that of a

unitary, integrated organism. Whether an argument on gestalt isomorphism should even be entered into is a mute point. The mere fact that Gestalt isomorphism, i.e., the idea of a functional correspondence between brain processes and their correlated percepts (31,32), forms an integral part of their approach should surely be enough to accept that they saw mind and body as a unity.

With the many prominent psychologists from the school of psychoanalysis it is rather difficult to summarise one specific position for psychoanalysis on the mind-body dilemma. It is therefore perhaps suffice to confine the discussion to the approach of Sigmund Freud (1856-1939) as founder. Freud himself declared his approach as psychophysical parallelistic - and therefore as dualistic, but according to Jones (33 in 34) different passages from Freud could alternatively put Freud in any of a number of philosophical mind-body positions. Apparently not taken into account when classifying Freud's position with regard to the mind-body connection, but relevant to some present day mind-body positions, is his work on the role of childhood experiences and genetics. In considering this, as well as his occupational training, one would expect to classify Freud under the compromise approaches. There would, however, appear to be general consensus that Freud, and most other psychoanalyst fit best in some form of dualism (34).

In the above short historical overview very little was said about the history of the American perspective on the mind-body situatedness. One name that has, however, been mentioned, i.e., that of William James (1842-1910), who can surely be considered as one, if not the, most important figure in search of the mind-body connection over that period. Author of several books and articles, including *Principles of Psychology*, 1890 (36), *Exceptional Mental States*, 1896 (37), *Varieties of Religious Experiences*, 1902 (38), *Does Consciousness Exist?* 1904 (39), *Philosophical Conceptions and Practical Results*, 1898 (40) and *Pragmatism, A New Name for Some Old Way of Thinking*, 1906 (41) James is today still considered as one of the most eminent American thinkers in the field. Although he is said to have anchored the study of consciousness to experimental physiology (35), he later went on to formulate a philosophical epistemology intended to diminish the supremacy of scientific materialism. Despite his many contributions James

never really committed to a definitive point of view on the mind-body problem. It can at best be said that he settled provisionally, in a rather tentative way, on a pragmatic empirical parallelism.

The previous paragraphs gave a synoptic overview of the history of the mind-body dilemma. It is perhaps easier to view this history in context to other developments, including that of the biological and other sciences. As such a discussion would be way beyond this introductory writing a chart has been compiled (Figure 1.1, p14) which facilitates the contextual understanding of the various developments on the mind-body association. The information incorporated into Figure 1 was extracted from a comprehensive document by Wozniak, 2002 (35), based on the catalogue accompanying an exhibition of books from the collections of the National Library of Medicine held in honour of the Centennial Celebration of the American Psychological Association. As the references were taken directly from the catalogue of the exhibition they are, for interest sake, included as an appendix to the normal reference list at the end of this chapter.

1.2 Cross-cultural perspectives on the mind-body situatedness

The previous paragraphs focussed on what could perhaps largely be seen as a historical perspective on the mind-body association from a Westerner's point of view. It would, however, be wrong not to touch upon some cross-cultural perspectives before attempting to summarise some of the major current Western First World views on the mind-body relationship. The different approaches of the various cultures to the mind-body connection are often totally intertwined with their religious practices. In scanning cross-cultural perspectives it becomes clear that language, symbols and the perception of the words *consciousness* and *mind* are other major determinants of the mind-body perspectives of specific cultures.

THE MIND-BODY PROBLEM FROM DESCARTES TO FREUD

Mind, Brain and Adaptation:
The Localization of Cerebral Function

Many of the Old Greeks already saw the brain as the centre of mental activity, but various other views about the localization of mind existed, including that of the pneumatic physiologists in which mental capacities were said to reside in the fluid of the ventricles and the Tabula Rasa point of view that saw the psyche of the neonate as a blank sheet written on by sensory experience.

The 19th Century witnessed the rise of the functional localisation proper (specific mental processes became associate with discrete brain areas)

Franz Josef Gall (1758-1828)
Anatomie et physiology du système nerveux en général (Gall and Spurzheim, 1810) (12)
The correlational approach of localization.
They described the cranioscopic method of locating mental faculties (correlations of variations in external craniological signs with character).

Several workers subsequently tried experimentally to localize function through lesioning by trephine aperture but the damage to the brain was too severe to make proper associations.

Marie-Jean-Pierre Fluorens (1794-1867)
Recherches expérimentalis sur les propriétés et les fonctions du système nerveux (1924 ed1,1942 ed2) (13).
Redefined experimental function-localisation coupling by uncovering area to be ablated with less damage.
Articulate difference between perception and sensation and localized sensory functions in sub-cortical areas. Postulated that higher brain functions occur as integrated function of cerebrum.

Alexander Bain (1818- 1903)
The senses and the intellect (1855)
The emotions and the will (1959) (14).
Defined sensory-motor associationism.
Paved the way for functionalist psychology of adaptive behaviour.

Herbert Spencer (1820-1903)
The Principles of psychology (1855) (15)
Evolutionary psychophysiology.
After reading Lewes become interested and eventually grounded psychology in evolutionary biology with key principles of cerebral adaptation, continuity, and development defined mental phenomena as adaptations. His key words: adaptation, continuity and development.

Paul Broca (1824-1880), Gustav Theodor Fritsch (1838-1927) And Eduard Hitzig (1838-1907)
Remarques sur le siége de la faculté du langage articulé, suivies d'une Observation d'aphemie (Broca, published in Bulletins de la Société Anatomique De Paris,1861) (16). Ground breaking paper published in Archiv für Anatomie, Physiologie, und wissenschaftliche Medicin (Fritsch &Hitzig1870).
Electrophysiology as technique (galvanic) for experimental exploration of function localisation.
This paper overturned the idea that functional localisation of the brain function was not possible. Provided the necessary experimental techniques and research findings for the extension of sensory-motor associationism and evolutionary psychophysiology to the cortex and identified a number of anatomical-functional relationships pertaining to the cortex.

John Hughlings Jackson (1835-1911)
Writings of John Hughlings Jackson (2 vols 1931, 1932)
Clinical and Physiological Research on the Nervous System (1875) (17).
Milestone in the integration of associative psychology with sensori-motor physiology.
A physician whose sensori-motor research focussed on clinical and physiological research. Speculated that all mental symptoms must be the result of lack of, or disorderly development of sensori-motor processes.

David Ferrier (1843-1928)
Experimental researches in cerebral physiology and pathology (a paper in: West Riding Lunatic Asylum Medical Reports, 1873), The Functions of the Brain (1876) (18).
Confirmed the work of Jackson by controlled ablation and Faradic stimulation.
Helped to confirm sensori-motor analysis as basic explanatory medium in both psychology and physiology.
Psychologist , at Heidelberg at the same time as Helmzholtz and Wundt (1964) and as physician, initially as assistant to Laylock, who articulated unconscious cerebration, Influenced by Spencer, Bain and Jackson.

Idea of soul related to brain found in work of Pythagorus, Hippocrates, Plato, Erisistratus, Galen, others

René Descartes (1596-1650)
French mathematician, philosopher, physiologist
De homine (1), Meditationes (2) and Les Passions de l'ame (3).
Father of the dualistic ((two-substance) view of mind and body (Cartesian impasse - the metaphysical split between mind and body).
First systematic account of mind/body relationship saw pineal gland as the contact between the body and the soul. Showed that body influences mind and mind influences body.

17th Century Reaction to Dualism of Mind and Body

Géraud de Cordemoy
Le discernement du corps et de l'ame (1666)
Preceding influence on occasionalism.

Nicolas Malebranche (1638-1715)
De la recherche de la vérité (4).
Most important influence of occasionalism.
Mind as well *as body is causually ineffective and can't influence* each other - God is the only true cause of experience.

Benedictus de Spinoza (1632-1677).
De ethica in his *Opera posthumus* , 1677 (5)
Rejecting Cartesian interactionism, coined double-aspect theory.
Mental and physical are simply different aspects of the same substance the substance being God which is the universal essence of everything. Mind can't influence body and body can't influence mind, but they are coordinated and connected by the Divine Influence.

Gottfried Wihelm Leibniz (1646-1716)
Système nouveau de la nature (1695) Eclaircissement du nouveau sisteme (1696)
Psychophysical parallelism of mind-body theories.
Retains dualistic separateness but with correlation between the two. Rejected interactionism (mutual influence) as well as occasionalism (a third regulatory influence) in favour of parallelism (primarily created to operate in unison) as source of the mind-body correlation. In this he saw a divine influence but at creation rather than on a continium.

18th Century: Mind, Matter and Monism

George Berkeley (1685-1753)
A treatise concerning the principles of human knowledge (1710).
Immaterialism (matter is only a perception)
There is no mind-body distinction the body is merely the perception of the mind. (This is to resurface as *mind-stuff* in the 19th century).

Julien Offray de la Mettrie (1709-1751)
Histoire naturelle de l'ame (1745), L'homme machine (1748) (6)
Materialism (matter is fundamental mental events causally dependent on bodily events)
Voluntary processes and conciousness can only be distinguished from involuntary instinctual processes by the complexities of their underlying mechanical substances. (Extreme version: Partially extended the concept of physical automata, as ascribed to animals by Descartes, to humans; Moderate version: mental processes not reductionistic related to neural processes).

Pierre Jean Georges Canabis (1757-1808)
Rapports du physique et du moral de l'homme (1802) (7)
Most ardent materialist of the French enlightenment.
Saw the brain as special organ designed to produce thoughts.

19th Century: Mind and Brain

Mind-body problem a central interest with emphasis on:

Progress in understanding the localisation of cerebral function

Mental believes, that suggestions, mesmeric trance states, psychic trauma, etc, can change the body

Most of the major theories of the 19th century (epiphenomenalism, interactionism, dual-aspect monism, mind-stuff) are variations on previous mind-body theories generally intended on dealing with the Cartesian impasse.

Shadworth Holloway Hodgson (1832-1912)
The theory of Practice (1870) (8)
First modern description of epiphenomenalism.
Mental states seen as non-causal by products (epiphenomena) of body incapable of reflecting back to influence nervous system.

Thomas Henry Huxley (1825-1895)
On the hypothesis that animals are automata and its history (1874)
Principles of Mental Physiology (1874) (9)
Popularised the epiphenomenalistic view
States of consciousness are merely the result of molecular changes in brain substance upon attainment of the prerequisite degree of organisation - supporting nervous system is independent of accompanying mental state.

William Benjamin Carpenter (1813-1885)
Principles of Mental Physiology (9)
Said to be foremost proponent of interactionism.
Convinced of a causal relationship between the brain and mental states such as consciousness, sensations, instinct and emotions on the one hand and cerebral (electrical) activity on the other. (Corresponds more to materialistic monism).

George Henry Lewes (1817-1878)
Biographical History of Philosophy (1846)
Physiology of Common Life (1859/1860), Problems of Life and Mind (1874-1879) (10)
The Physical basis of the Mind. In: Problems of Life and Mind (1874-1879) (10)
Father of classic modern dual-aspect monism (neutral monism).
His version of the double-aspect view is known as neutral monism, i.e., there is only one kind of substance (stuff) mind and body differ only in the arrangement of the "stuff" or in the way it is perceived. Mind and body are thus different aspects of the same psychophysical process. He did, however, argue against extreme reductionism.

William Kingdon Clifford (1845-1879)
On the Nature of Things in Themselves (published in Mind, 1878)
Coined the term:Mind-Stuff. Mind-Stuff monism is the position of psychical monism.
where the mind is the only real substance.
Kingdon put together the bits and pieces on the ideas of mind-stuff Pieces of brain material (mind-stuff) forms consciousness (they do not in themselves contain consciousness) - mind is the only actual substance and the material world is nothing more than an aspect in which mind is apprehended.

Morton Prince (1854-1929)
The Nature of Mind and Human Automatism (1885) (11)
Mind-Stuff theory. Gave the clearest exposition on the mind-stuff position.
He saw the psychical monism of mind-stuff as a modern form of immaterialism.
"There is only one substance, mind ; and the other apparent property-------".

Williams James (1842-1910)
The Principles of Psychology (1890)
Settled in a rather tentative way on a provisional pragmatic empirical parallelism.
Having critisized the automaton theory and the mind-stuff approach he declared himself reluctant to commit to any unsafe hypothesis.

Trance and trauma: Nervous System Disorders and the Subconscious Mind

Over 100yrs psychological studies showed that mental events Including suggestions, mesmeric trance states, psychological trauma, catharsis, emotional trauma, and submergence of part of the consciousness into the subconsciouss can dramatically influence the body

Franz Anton Mesmer (1734-1815)
Mèmoire sur la dècouverte du magnétisme animal (1777) (19)
Magnetism as basis for treatment
Believed that a physical magnetic fluid connected everything, including the human body and that physicians could redirect the magnetic flow if disturbed. His work discredited by Bailly and his own failures.
Rapport des Commissaires chargés par le Roy de l'examen du magnétisme animal (Bailly JS (ed). Paris: Imprimerie Royale, 1784).

Armand-Marie-Jacques de Chastenet, Marquis de Puysegar (1715-1825)
Mèmoires pour servir a l'histoire et a l'établissement du magnétisme animal (1784) (20).
Said by many to be the father of modern psychotherapy.
Disciple of Mesmer. Concluded that the effects of magnetism on patients, depend on the therapist's personal belief in the effectiveness of the treatment, the will to cure and on the interaction between the therapist and the patient. Developed technique for the induction of a somnambulistic sleep state where the patient carried out the orders of the therapist without any memory of it at awakening. Mesmerism (developed/described by Puysegar, comments by Mesmer) rapidly spread through Europe and USA.

Charles Poyen de Saint Sauveur
Spread mesmerism from France to Europe, evolving into the New Thought Movement.

Europe
Abbe Jose Custodio de Faria, Etienne Felix, Baron d'Henin de Cuvillers, Alexandre Bertrand, General Francois Joseph Noizet, James Braid.

Abbe Jose Custodio de Faria
De la cause du sommeil lucide (1819)
Developer of the trance-induction method. First articulated power of suggestion.
Stressed importance of patient's will to undergo somnabulistic sleep and interindividual differences.

Alexandre Bertrand
Traité du somnambulisme (1823)
First attempt at systematic scientific research into magnetic phenomena.

General Francois Joseph Noizet & Hènin de Cuvillers
Memoire sur le somnambulisme & Le magnetisme éclairé (1854).
Described in more detail mesmeric effects in terms of suggestion and believe.

James Braid (1795-1860)
Neurypnology: or, the Rationale of Nervous Sleep, Considered in Rationale with Animal Magnetism (1843) (21).
Father of hypnotism.
Desribed physical signs of mesmerism to be a state of he nervous system due to *fixed and abstracted* attention. Coined the name *hypnotism* to distinguish it from *magnetism*.

Period of transient decline of hypnotism circa 1860 +
(Ellenberger H. Discovery of the unconsciouss. Basic Books,1970)

Auguste Ambroise Liébeault (1823-1904)
Du sommeil et des etats analogues consideres surtout au point de vue de l'action du moral sur le physique (1866) (22).
Kept the idea of hypnosis as therapeutic tool alive through period of decline.
Extracted from the writings of Noizet and republished the idea that therapeutic effects of hypnosis should be seen as suggestive phenomena. Lived near Nancy and his work was later to revive the interest in hypnosis of the founders of the School of Nancy.

Charles Richet
Du somnanbulisme provoqué (1875).
Scientific basis of hypnosis.
Physiologist said to have saved hypnosis from being a pseudoscience. Work became the basis for the research of others like Charcot.

Jean-Martin Charcot (1825-1893)
Leçons sur les maladies du système nerveux à la Salpêtrière (1872-1873) (23).
Founder of the world's foremost institute of neurology at the Salpêtrière.
Influenced by the work of Richet and Briquet (who wrote the first systematic study on hysteria,1859) distinguished, through hypnosis, between symptoms which arise from brain lesions and those which results as a result of suggestive, hysterical and post-traumatic phenomena . Articulated the existence of unconscious ideas as basis of neurosis. Contributions marred by believe that transference occurred through magnetism.

Hippolyte Bernheim (1840-1919)
De la suggestions dans l'état de veille (1884,1886) (24).
Conceptualized hypnosis as manifestation of ideomotor suggestibility - opposed the view that magnetism plays a role. Founder member of Nancy School of suggestive therapeutics.
Influenced by work of Liébeault during his appointment as physician at the medical faculty at Nancy. Believed somatic hypnotic effects to be mediated through suggestions & hypnosis, being a state where high prolonged suggestibility is induced. Members of the School of Nancy abandoned hypnotism in favour of suggestion in the waking state, i.e., "psychotherapeutics".

Pierre-Marie-Felix Janet (1859-1947)
L'automatisme psychologique (25), and other writings.
Articulated the dissociaton of consciousness, relevant mental disorders and somatic symptoms.
Employed automatic writing and hypnosis to enter the patients "automatisms". Distinguished mental states on the basis of consciousness and submergence into the subconscious. Stressed the role of patient's fixation on, and rapport with, therapist as well as patient's perception.

Joseph Breuer (1842-1925) and Sigmund Freud (1856-1939)
Ueber den psychischen Mechanismus hysterische Phänomene (1893) (26).
Beginning of psychoanalysis.
Catharsis involving guided associations to bring past trauma events into consciousness in an attempt to cure the mental and associated somatic symptoms.

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KEY

Major contributions
Publications

Figure 1.1: Developments in the mind-body concept from Descartes to Freud

In the middle column the major contributors to the developments from Descartes to James are shown. The column on the left illustrates the developments in the localisation of cerebral functions during the 19th century and the column on the right shows the developments in the concept that mind states can influence somatic functions - more or less during the same period.

Some of the cross-cultural views were reviewed by Krippner, 1994 (42). Krippner (42) pointed out that many cultures don't differentiate between body and mind and that some cultures do not even have a separate word for *mind*. In fact, while Eastern, as well as some of the early South American cultures may be able to eloquently define altered states of consciousness as part of normality, Western cultures generally tend to see such experiences in terms of psychopathology.

Without going into any detail, and without pretending to any in depth comprehension of the mind-body views of other cultures, at least the following examples warrant mentioning:

- Buddhism, where volumes have been written on the mind-body interaction, especially with regard to meditative practices, and much time was and still is being devoted to the contemplation of mind and body. It is said that Buddhism sees the mind as a highly refined field of energy (43). This view approaches that of the models of modern physics. Whether the assumption that Buddhism sees the mind as a highly refined field of energy comments on the mind-body relationship is questionable as a sense of biological consciousness and emphasis on the concept of integration of mind, body and spirit permeates most of the writings on Buddhism available in English. The Tibetan Buddhist philosophy, its classification of the mind states, and the systems of meditation practices and levels, are aimed at achieving ideal states of being and need dedicated involvement to be really understood. Reaching for the ideal mind/body integrated state does, in fact, represent the life-long occupation of many Buddhists.
- The approach of the Huichol, i.e., a Mexican tribe whose views of consciousness and mind-body relationship strongly reminds one of that of some of the Eastern philosophies in the sense that they see the physical world as an illusion, and reality as a state not understood by the normal awake mind. The Huicol approach is, in this writing, referred to as an example of a cross-cultural perspective that bears some resemblance to monistic phenomenalism. It is said that the Huicol spend the majority of their lives in a kind of well-organised hallucination (42,44). Some similarity is found in South Africa where the Rastafarians use dagga in order to reach the desired mind state.

- Shamanism, a spiritualism practiced by certain North American Indian tribes, and by certain groups in Northern Asia, is known for, what is seen in Western cultures, out-of-body experiences. The Shaman concept of the *dreaming body*, that is said to have the ability to move into different realms, is seen, not as an out-of-body experience, but merely as a transient shift into another body more suitable for the task at hand (42). This would in Western cultures most probably be classified as psychopathology. One should, however, first ask whether any resemblance exists to some present day mind-body practices or even to some forms of psychotherapy, before berating them. It is important to remember that shamanism is found in Central Asia, amongst the Chinese, the Japanese, the Maori and even in Tibet, and that each region has its own variation on the general theme (45).
- Other mind-body models that, to a degree resemble monistic viewpoints, but where the ideas of reality and consciousness differ markedly from our conventional Western understanding, include the Mayan and the Aztec models (44, 46). The idea of the Aztec model being of a monistic nature is, however, somewhat belied by what is recorded as a willingness to die in order to attain the status of a liberated spirit. This concept of liberation of the spirit is not unique to the Aztec model as others, including the Australian Aborigines, are said to have their own particular practices in order to obtain this experience during their so-called primordial dreamtime (42,44,46). Some groups in Central America believed in the existence of a *counterpart in disguise.* This counterpart, often disguised in the form of an animal, was believed to have had its fate linked to that of the human through the influence of cosmic forces (46 p66).
- Other related cross-cultural variations on the mind-body position include a) the consciousness model derived from the practices and believes of Brazilian natives where each of ten bodily centers, respectively, is said to control a specific aspect of the mind-body interaction, b) the view amongst traditional Hawaiians where the physical body and three other bodies, i.e., an etheric body, an astral body and a mental body, exist, as well as a mind that can be active at the conscious, the unconscious and the superconscious level and c) the view of the Huna which considered the body to be in the mind, but the mind to be only partially in the body (42,44,47).

- Amongst the Hindu-related spiritual practices various approaches to the mind-body position exist (48). It would appear as if most of them, in common with Tibetan Buddhism, adhere to the principle of indivisibility of mind and body (48,49). It is, however, very difficult to define the term Hinduism and the above statement may not apply to all Hindus. Therapies based on Eastern mind-body unity approaches, including the so-called Eastern movement therapies tai chi, qigong and yoga, are increasingly being incorporated into Western health practices in an attempt to reach unification of mind and body (42,50). The best-known techniques adopted by the West are probably the various forms of meditation. They do not need further discussion at this point.
- The Ayurvedic approach sees mind and body as an inseparable unity where the highest levels of spiritual development are said to require a healthy body. This is referred to separately from Hinduism as those for whom the Vedic heritage represents the main expression of religion are not classified as strictly Hindu – rather as pre- or proto-Hindu (48). Ayurveda shares the principle of balance of life forces with that of Chinese and some Buddhist approaches (48,50). A commercialised version of Ayurveda has recently become the vogue, as well as big business, in the West. The mind-body view of this variation on Ayurveda would appear to approach the mind-stuff version of monism (Deepak Chopra, lecture, Johannesburg, 2002).

Although glimpses of African considerations on the mind-body paradox can be gleaned from books such as Credo Mutwa's *Indaba My Children* (51) and Parrinder's Man and His Gods (52), no recent text could be found with the focus primarily on the mind-body approaches of the various indigenous people of Africa.

In conclusion it can be said that some of the cross-cultural perspectives just discussed would in the First World of today surely be seen as psychopathology. There are, however, similarities to be found between the cross-cultural views and some of the historical Western perspectives - even to some of the perspectives currently adhered to. Although the mind-body approaches of the school of psychoanalysis were, but for Freud, not touched upon in the section that dealt with the historical perspectives, there would

appear to be an eerie resemblance between some of the cross-cultural views and certain concepts from the school of psychoanalysis. It would be foolish to summarily denounce these cross-cultural views as inferior to that of the First World as many analogies may be found when analysed in context of their respective social environments.

1.3 Current views on the mind-body relationship

The majority of First World Westerners would appear to adhere to some kind of monistic view of the mind-body relationship, but variations on the dualistic approach, as well as a variety of compromises between the two exist. In addition various cross-cultural perspectives are still alive and well and, as previously mentioned, more attention is currently being paid in the West to mind-body approaches and practices based on Eastern philosophies.

The dualistic approach is still vigorously adhered to by those considering the differences between the brain and the behavioural processes as irreconcilable. Although most present day dualists accepts the reality of an interaction between mind and body, no feasible interactive pathway could yet be offered in explanation for the link between the material body and the presumed immaterial mind. Some vague, rather unsatisfactory, explanations were put forward by Karl R Popper, 1977 (53) and John C. Eccles, 1989 (54). Another form of dualism is found among many individuals from diverse religious persuasions, i.e., occasionalism where the mind and body is seen as separate and independent, but correlated by the intervention of God.

The monistic approach can rightfully be seen as the major academic concept of the day - at least where the First World is concerned. The majority of current day monists are materialists, believing that the processes of the mind are of material origin, inseparable from the brain and subject to the same physicochemical laws as everything else. Two other forms of monism are, however still adhered to by smaller groups, i.e., subjective idealism, which proclaims a single underlying mental reality to mind and body, and phenomenalism, which proclaims that neither mind nor body exists – only impressions.

Over the past 50 years empirical scientists from various disciplines had significant success in identifying the so-called mechanisms underlying the processes generally seen as mind (55,56,57,58,59). The empirical research activities of these scientists, often from diverse disciplines, have come to be known as the *analytical philosophy of the mind.* In this school of thought it is accepted that no mind exists without the physical brain and the only problem that remains is to identify the exact underlying processes.

In the quest to define materialistic-monism in terms of evolution the Darwinian evolutionary theory evolved into the post-Darwinian theory where the properties of the mind are seen as the evolutionary development of ever more complex neural networks. Developments in the post-Darwinian evolutionary theory lead to the concept of *emergence*, a term referring to the identification or emergence of previously unknown characteristics of, amongst others, the brain. Several variations exist on the *emergence* monistic approach with one of the more reductionistic-materialistic variations found in the *identity hypothesis* (60). The identity hypothesis sees mind and brain as one – a kind of function-structure relationship - interpreted by some as the elimination of mind (61). The reductionistic materialistic version of the monistic approach left us with the problem of the *freedom of will* and the question of *determinism.* The determinants of *the freedom of will and action* is at this period in time still passionately debated and approaches vary from a) the purely neurophysiological view of Kornhuber, 1978 (62), where mind is reduced to the flow of information through the nervous system, to b) the *logical relativity principle* of MacKay, which virtually denies the existence of free action (63), to c) the evolution-based concept of Searle, 1984 (64), that claims evolution to have provided mankind with conscious, voluntary and intentional behaviour, to d) approaches based on pure physics like the holographic paradigm proposed by Pribram and Bohm, 1991 (65), and the so-called computer paradigm described by Beckerman, 1990 (66), based on the argument that even non-living physical systems such as computers can come to logical conclusions, and to e) sub-molecular level arguments and quantum physics to f) multidimensional perspectives, such as that of Halstedt, 1988 (58), that proposes the mind to be part of nature which, in line with the emergence theory, has acquired the ability to think and to reflect. An outflow from the sub-molecular search into the meaning

of mind is the return to another form of monism, i.e., subjective idealism – although not presently referred to as such. It is said that elementary particle physics has become so abstract that its objectivity is disappearing – leaving the concept of matter and the principle of causality disputable (61). Based on this the mind is suggested to be the deepest sense of reality from which the body emerges in some or other way (67). The natural sciences, in moving into this abstract sub-molecular level of elementary particle physics, finds itself in the same dilemma as that of the humanities where the safe foundation of empirical evidence becomes extremely elusive.

One can perhaps summarise by saying that the materialistic version of the monistic approach to the mind-body dilemma is the view of the day but that many questions still bewilder us, not least the question of free will and determination. However, the study of consciousness remains a stumbling block as no general agreement can be reached on the meaning of this concept. To quote Miller, 2000 (68):

Classical science, alternative and complementary healing, quantum physics, and metaphysics all take drastic different approaches to consciousness research. A bridge is needed to restore the conceptual unity of mind-body. However the construction of such a bridge paradoxically must rely on consciousness for information. The construction company (Consciousness, Inc.) therefore becomes means and end in the design of the bridge.

Miller, 2000 (68).

In *Journey to the Centers of the Mind* by Greenfield, 1995 (69) the author attempts to unify many of the apparently incompatible theories of consciousness ranging, from phenomenological perceptions to physical neural events, into a concentric theory of consciousness. Miller (68), five years later, would not appear to have read the work. In this lies another problem in the progression of our understanding, i.e., the lack of interdisciplinary efforts and communication – ironically referred to by Miller himself.

In accepting reductionistic-monism to be the approach of the day one should, however, emphasize that this view is not without opposition – not even within the usually materialistic-monism encountered in the field of medicine. An interesting point of view, coming specifically from a department of internal medicine (70), and based on the fourth century writings of Gregory of Nyssa (71), recently appeared in *Perspectives in Biology and Medicine*, urging physicians not to fall into the traps of reductionism or idealism. It should in summary be stressed that certain contemporary approaches, currently being grouped under materialistic-monistic, strongly resemble compromises. In addition, various interdisciplinary attempts in search of a model that unifies the concepts from the major prevailing schools of thought are presently in progress. It would, however, appear that the majority of scientist, from both the natural sciences and the humanities, accept the integration of mind and body without questioning the definitive relationship.

Over the last two decades the so-called post-modern perspectives on mind-body unity have become objects of intense scientific research. Among these psychoneuroimmunology (PNI) is considered by many as one of the most important recent developments involved in the redefinement of the mind-body relationship. Psychoneuroimmunology is, however, less interested in what is considered the mind-body problem and more in the multi-directional interactions between mind and body. This, by implication, includes past and present environmental influences. In this respect it perhaps resembles groups from the school of functionalism who accepted the interaction or unity without further ado. In psychoneuroimmunology the focus is on the practical implications of the interaction rather than on the nature of the interaction.

Psychoneuroimmunology, in short, looks at behaviour as biological response modifier and *vice versa*. The next paragraphs will briefly define psychoneuroimmunology and attempt to put it in context to other paradigms.

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1.4 Introduction to Psychoneuroimmunology

Psychoneuroimmunology (PNI) is the study of the interactions between behaviour, the brain and the immune system. As the neurological system is largely in control of the endocrine system the interactions can be seen as between behaviour, brain, endocrine and immune systems. Psychoneuroimmunology is therefore sometimes also referred to as psychoneuroendocrino-immunology (PNEI). The immune system, previously seen as an independent system responding only to antigenic stimulation, is now known to be influenced by the neuroendocrine system. It is becoming more and more clear that the immune system can in turn act as neuroendocrine regulatory system. The immune system was, in fact, described by Blalock (72), as a sixth sense organ, informing the brain about peripheral events. The influence of the immune system on the brain is, however, much more than that of a sensory organ. It has, in addition, been shown to be able to alter cerebral functioning, and to induce long-term anatomical changes with subsequent behavioural effects. It speaks for it self that interactions between the behavioural functions and the two main physiological regulatory systems, i.e., the neuroendocrine and immune systems would influence the total individual – mind as well as body. Every system and function would therefore influence, and be influenced by, all others. In addition, perceptions of environmental events registered through the senses, information about inflammatory or infectious conditions carried by immunological messenger systems, and psychological events with its associated patterns of cerebral information flow, would all be able to influence, and be influenced by, the functional integrity of both body and mind.

Many devoted scientists in a variety of sub-disciplines contributed to the rapid conversion of psychoneuroimmunology from a speculative field to that of a recognised science. The idea of the psychoneuroimunological interaction being a recent concept is, however, wrong. All that is new is the name and the scientific credibility afforded to the existence of the interaction – this as a result of the intense research by accredited scientists of recent times. Written proof for earlier acceptance of this kind of mind-body interaction, or rather unity, can be found throughout the literature. In scanning the historical, the

cross-cultural, as well as more recent approaches to the mind-body problem, it is clear that the concept of a mutual influence between the psychological and physiological functions were taken for granted by most - this despite differences in their positions to the mind-body impasse. In Figure 1.1, right column, it was seen how, over a period of about 100 years, psychological studies showed that mental events such as suggestions, mesmeric trance states, trauma, catharsis, and submergence of part of the consciousness into the subconsciousness can dramatically influence the body. However, recognition of the mind's potential influence on the body existed long before the existence of psychology as a subject. Suffice to refer to the Transylvanian physician Papai Pariz Ferenc (73), said by Solomon in 1993 (74), to essentially have reiterated Aristotle and to have anticipated psychoneuroimmunology when, in 1680, he wrote:

When the parts of the body and its humors are not in harmony, then the mind is unbalanced and melancholy ensues, but on the other hand, a quiet and happy mind makes the whole body healthy.

Papai Pariz Ferenc, 1680 (73).

Although intuitive knowledge about the interactions between the psychological status and inflammatory, as well as infectious, conditions has been there for literally hundreds of years, the academic knowledge to prove this link was lacking. From an academic point of view it is obvious that psychoneuroimmunology evolved from observations that a connection exists between psychological stressful events and disease. In fact, psychoneuroimmunology can rightfully be seen as an outflow of the stress paradigm. Another trailblazer, albeit lesser investigated in terms of the underlying mechanisms, and perhaps more of a postulate than a scientific proven field, is the biopsychosocial approach. More direct empirical evidence in support of the interactions were derived from a sub-discipline of the biological sciences, i.e., neuroimmunomodulation. Although initial papers on psychoneuroimmunology were speculative (75), we have now moved beyond the point of speculation and intuitive knowledge to where the convergence of many sub-disciplines from the biological sciences and humanities lead to the emergence of its present status, i.e., an interdisciplinary field where body and mind are seen as one

functional unit. Many workers from various disciplines contributed to the development, but the names of Robert Ader[1], David L Felten[2] and Nicholas Cohen[3] (76,77,78) should be mentioned for their outstanding contributions in converting psychoneuroimmunology to a recognised scientific field.

Despite the current intense focus by some on psychoneuroimmunology, the majority of scientists, in both the humanities and in the natural and medical sciences, are still not familiar with, or even sceptical about, the field. This is largely based on ignorance as well as a blatant disregard for the obvious. A major contributing factor may be the diverse nature of the interacting academic fields, i.e., psychiatry, psychology, immunology and neuroendocrinology.

Before buying into the psychoneuroimmunological concept it would be reasonable to ask what practical examples could be found in order to corroborate the existence of the psychoneuroimmunological interaction. The answer lies in at least three major categories of evidence, i.e., a) the fact that the immune system can be conditioned to react in a specific way, b) the influence of behavioural factors and psychological interventions on the clinical course and outcome of disease processes and c) the behavioural changes which follows upon immune-associated physical disorders and upon administration of immunocompetent substances such as cytokines.

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[1] Editor-in-Chief of *Brain, Behavior, and Immunity*, editor/co-editor of all three editions of *Psychoneuroimmunology*, past president of the *American Psychosomatic Society*, the *International Society for Developmental Psychobiology* and the *Academy of Behavioral Medicine Research,* and founding member of the *Psychoneuroimmunological Society.*

[2] Past director of the *Neurosciences Graduate Program* and associate director of the *Center for Psychoneuroimmunological Research* at Rochester University, co-editor of *Psychoneuroimmunology* 2nd and 3rd editions, associate editor of *Brain, Behavior and Immunology*, and present director of the *Center for Npecteuroimmunology* at the Loma Linda University School of Medicine.

[3] Professor of *Microbiology and Immunology,* associate director for *Psychoneuroimmunological Research*, past councilor of the *Psychoneuroimmunological Research* Society and co-editor of the 2nd and 3rd edition of *Psychoneuroimmunology* .

1.5 Organisation of subsequent chapters

The aim of this thesis, as previously mentioned, is to define the psychoneuroimmunological interaction in terms of the two main stress axes. Before embarking on a description of the various intercommunications it is necessary to have empirical evidence in support of the existence of a pervasive psychoimmunological interaction and to show that this bidirectional influence has practical implications for both the psychological and physical health of the individual. The next chapter, i.e., Chapter 2, will deal with such evidence. It will also be shown that immune changes have been reported for all classes of the DSM-IV. Reference will be made to the biopsychosocial model mentioned in Chapter 1. This aspect will be returned to in Chapter 7 where it will be shown how the psychoneuroimmunological concept relates to, but also differs from the biopsychosocial model.

The subsequent three chapters will provide the necessary evidence for the bidirectional influences between the psychological, the neurological and the immunological aspects, i.e., the empirical proof for the psychoneuroimmunlogical interactions in terms of the two main stress axes. As was previously mentioned, psychoneuroimmunology is considered an extension of the stress paradigm. This becomes markedly evident when the controlled stress response is seen as a new homeostasis in which mind and body are empowered to cope with the stressor – be it physical or psychological. In fact, it will be seen that the classification of stressors into psychological and physical is artificial and only applies to the initial stimulating event as mind and body, respectively, are influenced by each other in a transactional manner. In this thesis stressors and stress are treated as integral aspects of everyday life, necessary for growth, development and adaptation – with the concept of psychopathology entering the quotation only when normal control is overpowered or negative feedback fails.

In line with the aim of the thesis Chapters 3 to 5 will present the psychoneuroimmunological interactions of the two main stress axes. Chapter 3 and 4 will deal with psychoneuroimmunology in terms of the first major stress axis, i.e., the central

noradrenergic/sympathoadrenomedullary axis. In Chapter 3 the importance of this system for the regulation of states of cognition, emotion and cerebral activity will be shown, as well as its interactions with other neuromodulatory systems that are major determinants of the psychological disposition and responses. Chapter 4 will show that these same neuromodulatory systems, so important in the psychological processes, can influence and be influenced by the immune system. Chapter 5 will deal with the psychoneuro-immunology of the second stress axis. The interactions will again be shown between the psychological and the cerebral aspects, and between the neurological and immunological functions. It will be shown that corticotropin releasing-hormone (CRH) plays a central role in the psychoneuroimmunological interaction with regard to both stress axes. This will be illustrated diagrammatically. Having demonstrated the controlling role of CRH in the psychoneuroimmunological interaction of both stress axes, Chapters 6 and 7 will, when referring to the neurohormonal aspects, focus primarily on the corticotropin-releasing hormone/hypothalamo-adrenocortical axis.

Chapter 6 will discuss mechanisms through which immunological activity can influence the neurological and therefore the psychological status – with particular emphasis on the immune influence on CRH/HPA-related behaviour. It will be shown that immunological events can act as stressors, leading to a new adaptive neuropsychological homeostasis.

Chapter 7 will present a model comprising relevant psychoneuroimmunological interactions to demonstrate the influences discussed in the rest of the thesis. A model of sickness behaviour, developed to demonstrate psychoneuroimmunology in terms of the two main stress axes, will be presented. It will be shown how psychosocial, as well as immunological events during early life can predispose to, and prolong erstwhile appropriate adaptive sickness behavioural responses and how this can lead to inappropriate, prolonged behavioural symptoms that correspond to that of psychiatric disorders.

Chapter 8 will present concise conclusions on the thesis as a whole.

In an attempt to facilitate the reading of the thesis a synopsis of each chapter is given in bold at the start of each chapter. This should be seen as an abstract of the chapter. Each chapter is again concluded by a short explanatory writing, given in bold, that connects it to the subsequent chapter. Due to the interdisciplinary nature of the work Chapter 4 and part of Chapter 5 (neuroimmunological interactions) have a very strong physiological bias. For the purpose of this writing presentation of integrated diagrams would probably have sufficed. However, such diagrams do not exist and had to be compiled from publications. These diagrams are presented at the end of each chapter. It is possible to understand the diagrams without going through the chapters - should the reader not be interested in the supporting evidence for the interactions shown in the diagrams.

This chapter presented a very brief overview of the mind-body problem, first in historical context, followed by examples of cross-cultural perspectives and a discussion of the more recent developments in the field. The major current perspective appears to be materialistic-monistic, which confronts us with several problems, not least the question of free will and determination. Psychoneuroimmunology, as so-called post-modern perspective on the mind-body relatedness, is defined and it is shown that its implications for mind and body were long intuitively suspected. The chapter is concluded with the rationale and layout of the rest of the thesis. The next chapter will show the pervasive bidirectional influence between the behavioural functions and the first of the two main stress axes, i.e., the central noradrenergic/peripheral sympathoadrenomedullary axis.

References

1. Bloom FE, Lazerson A. Introduction to the nervous system. In: Floyd E Bloom and Arlyne Lazerzon (eds), Brain, Mind and Behavior (2nd ed.), WH Freeman and Company, New York, 1988, pp13-18.

2. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.). McGraw-Hill Book Company, New York, 1987, pp32-34.

3. Plug C, Meyer WF, Louw DA, Gouws LA. Psigologiewoordeboek. Lexicon Uitgewers, Johannesburg, 1988, p292.

4. Duncan G. Mind-body dualism and the biophysical model of pain: What did Descartes really say? J Med Philos 2000;25:485-513.

5. Plug C, Meyer WF, Louw DA, Gouws LA. Psigologiewoordeboek. Lexicon Uitgewers, Johannesburg, 1988, p74.

6. Plug C, Meyer WF, Louw DA, Gouws LA. Psigologiewoordeboek. Lexicon Uitgewers, Johannesburg, 1988, p90.

7. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, p469.

8. Plug C, Meyer WF, Louw DA, Gouws LA. Psigologiewoordeboek. Lexicon Uitgewers, Johannesburg, 1988, p29.

9. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp40-71.

10. Joncich G. The sane positivist: A biography of Edward L Thorndike. Middletown, CT: Wesleyan University Press, 1968.

11. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, p487.

12. Plug C, Meyer WF, Louw DA, Gouws LA. Psigologiewoordeboek. Lexicon Uitgewers, Johannesburg, 1988, p351.

13. Wundt W. Principles of physiological psychology (Translated by EB Titchener). MacMillan, New York, 1910.

14. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp76-79.

15. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp83-88.

16. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp107-143.

17. Titchener EB. An outline of psychology. MacMillan, New York 1899.

18. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, p476.

19. Plug C, Meyer WF, Louw DA, Gouws LA. Psigologiewoordeboek. Lexicon Uitgewers, Johannesburg, 1988, p106.

20. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp112-119.

21. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp131-133.

22. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, p469.

23. Plug C, Meyer WF, Louw DA, Gouws LA. Psigologiewoordeboek. Lexicon Uitgewers, Johannesburg, 1988, p37.

24. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp145-188.

25. Watson JB. Psychology as the behaviorist views it. Psychological reviews 1913;20:158-177.

26. Weiss AP. Relation between structural and behavior psychology. Psychological reviews 1917;34:301-317

27. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp189-246.

28. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, p234.

29. Prentice WCH. The systematic psychology of Wolfgang Kohler. In S Koch (ed.), Psychology: A study of a science. (Vol. 1). Sensory, perceptual and physiological formulations. McGraw-Hill, New York, 1959, pp427-455.

30. Watson The great psychologists from Aristotle to Freud. (Rev ed), Lippincott, Philadelphia, 1968.

31. Henle M. Isomorphism: setting the record straight. Psychol Res 1984;46:317-327.

32. Scheerer E. Psychoneural isomorphism: historical background and current relevance. Philos Psychol 1994;7:183-210.

33. Jones E. The work and life of Sigmund Freud (Vols 1-3). Basic Books, New York, 1953, 1955, 1957.

34. Marx MH, Cronan-Hillix WA. Systems and theories in psychology (4th ed.) McGraw-Hill Book Company, New York, 1987, pp247-293.

35. Wozniak RH. Mind and body: René Descartes to William James. 2002. http://serendip.brywar.edu/Mind/Table.html.

36. James W. The Principles of Psychology. Henry Holt and Co 1890.

37. James W. William James on Exceptional Mental States, The 1896 Lowell Lectures. Charles Schribner's Sons, New York, 1983.

38. James W. The Varieties of Religious Experience, A Study in Human Nature (Clifford lectures). Longmans, Green and Co., New York, 1902.

39. James W. Does consciousness exist? Journal of Philosophy, Psychology and Scientific Methods 1904;1:477-491.

40. James W. Philosophical Conceptions and Practical Results. The University Press, Berkeley, 1898.

41. James W. Pragmatism, A New Name for Some Old Ways of Thinking. Longmans, Green and Co. London, New York, 1907.

42. Krippner S. Postmodern and cross-cultural perspectives on mind and body. International Journal of Psychosomatics 1994;41:81-86.

43. Jerry M. Psychoneuroimmunology. In: R Gregor and U Windhorst (eds). Comprehensive Human Physiology (vol 2), Springer-Verlag, Berlin, Heidelberg, New York. 1996, pp1731-1745.

44. Tomkins P. This tree growths out of hell. Mesoamerica and the search for the magical body. Harper, San Francisco 1990.

45. Parrinder G (Ed.). Man and his Gods: Encyclopedia of the World's Religions. Grosset and Dunlap, Madison Square Press, New York, 1971, pp21, 27, 41-43, 46-48, 308-327, 259

46. Parrinder G (Ed.). Man and his Gods: Encyclopedia of the World's Religions. Grosset and Dunlap, Madison Square Press, New York, 1971, pp63-85.

47. Schuster DH. Huna: A magic way of life. Photoprint, Carlisle, 1992.

48. Parrinder G (Ed.). Man and his Gods: Encyclopedia of the World's Religions. Grosset and Dunlap, Madison Square Press, New York, 1971, pp161-197.

49. Radha SS. Realities of the dreaming mind. Timeless Books, 1994.

50. Farrell SJ, Ross AD, Seghal KV. Eastern movement therapies. Phys Med Rehab Clin North Am 1999;10(3):617-629.

51. Credo Mutwa V. Indaba my Children. Vusamazulu Credo Mutwa and Blue Crane Books (Reprinted C Tingling), London and Prescot, 1973.

52. Parrinder G (ed.). Man and his Gods: Encyclopedia of the World's Religions. Grosset and Dunlap, Madison Square Press, New York, 1971.

53. Popper K, Eccles JC. The self and its brain. Springer, Berlin, Heidelberg, New York, 1977.

54. Eccles JC. Evolution of the brain. Creation of the mind. Routledge, London, 1989.

55. Blakemore C. Mechanics of the mind. Cambridge University Press, Cambridge. 1976.

56. Bieri P (ed). Analytische Philosophie des Geistes. Hain, Konigstein (Taunus), 1981.

57. Dennett DC. Brainstorms. Philosophical essays on mind and psychology. Harvester, Hassocks, 1979.

58. Halstedt H. Das Leib-Seele-Problem. Zwischen Naturwissenschaft des Geistes und kultureller endimensionalitat. Suhrkamp, Frankfurt/Main, 1988.

59. Joseph Le Doux. The emotional brain. Phoenix, Orion Books Ltd, London, 1999.

60. Borst CV. The mind-brain identity theory. MacMillan, London, 1970.

61. Henatsch HD. Psychomotor aspects of the brain-mind problem. In: R. Greger, U Windhorst (eds). Comprehensive human physiology. (vol 1). Springer-Verlag, Berlin, Heidelberg New York, 1996.

62. Kornhuber HH. A reconsideration of the brain-mind problem. In: PA Buser, A Rougeul-Buser (eds). Cerebral correlates of conscience experiences. Elsevier Biomedical Press, Amsterdam, 1978, pp319-334.

63. MacKay DM. What determines my choice? In: Buser PA, Rougeul-Buser A (eds.) Cerebral correlates of conscious experience. Elsevier Biomedical Press, Amsterdam, pp335-353.

64. Searle J. Minds, brain and science. The 1984 Reith lectures. Chapter 6: The freedom of will. Harvard University Press, Cambridge (Mass), 1984, pp86-99.

65. Pribram K. Brain and perception: holonomy and structure in figural processing. Erlbaum, Hillsdale, 1991.

66. Beckerman A. Monisms – Herausforderung an die Philosophie. Ist eine materialistische Analyse des Geistes Moglich? In: O-J Greusser, F Hucho (eds). Aus Forschung und Medizin, Streit um die Seele. Schering, Berlin, 1990, pp25-32.

67. Von Weizsacker CF. Die Einheit der Natur, part 111: Das Philosophische Problem der Kybernetic, Hansen, Munich, 1971.

68. Miller DW. Designing a bridge for consciousness: are criteria for unification of approaches feasible? Adv Mind-Body Med 2000;16(2):82-89.

69. Greenfield SA (ed.). Journey to the centers of the mind. Towards a science of consciousness. WH Freeman and Co., New York, 1995.

70. Bishop JP. Mind-body unity: Gregory of Nyssa and a surprising fourth-century perspective. PBM 2000;43(4):519-529.

71. Gregory of Nyssa. On the making of man. In: Gregory of Nyssa: The Nicene and Post-Nicene Fathers, (vol 5), translated by W Moore and HA Wilson. Eerdman's, Grand Rapids, 1988.

72. Blalock JE. The immune system as sensory organ. J Immunol 1984;1067-1070.

73. Ferenc PP. About the peace of the spirit. Transylvania, 1680.

74. Solomon GF. Whither psychoneuroimmunology? A new era of immunology, psychosomatic medicine, and of neuroscience. Brain Behav and Immunol 1993;7:352-366.

75. Solomon GF, Moos RH. Emotions, immunity and disease: A speculative theoretical integration. Arch Gen Psychiatry 1964;11:657-764.

76. Ader R, ed. Psychoneuroimmunology (1st ed.). Academic Press, New York, 1981.

77. Ader R, Felten DL, Cohen N. Psychoneuroimmunology (2nd ed.). Academic Press, New York, 1991.

78. Ader R, Felten DL, Cohen N. Psychoneuroimmunology (3rd ed.). Academic Press, New York, 2001.

Appendix

From the catalogue of the exhibit of books from the collections of the National Library of Medicine held in honour of the Centennial Celebration of the American Psychological Association.

1. Descartes, René (1596-1650) *Renatus Des Cartes de homine, figuris, et latinitate donatus a Florentio Schuyl* ... Lugduni Batavorum, apud Petrum Leffen & Franciscum Moyardum, 1662. 18 p.l.,121(i.e., 123),[1] p. illus. plates. 21 cm. [Written in 1633, suppressed, and unpublished before 1662.]

   ENGLISH: *Treatise of Man[.]* [By] René Descartes[.] French text with translation and commentary by Thomas Steele Hall[.] Harvard University Press[,] Cambridge, Massachusetts[,] 1972[.] xlviii, [2],232 p. illus. 24 cm.

2. Descartes, René (1596-1650) *Renati Des Cartes[,] meditationes de prima philosophia, in quibus Dei existentia, & animae à corpore distinctio, demonstratur* ... Tertia editio prioribus auctior & emendatior ... Amstelodami, Apud Ludovicum Elzevirium. 1650. 6 p.l.,191,[1] p. 20 cm. [Published with an:] Appendix, continens obiectiones quintas & septimas in Renati Des-cartes meditationes de primâ philosophia, ... altera ad celeberrimum virum D. Gisbertum Voetium ... [with a special titlepage] Amstelodami, Apud Ludovicum Elzevirium, M.DC.XL.IX [1649], [and separate paging,] 164 p. [and:] Epistola Renati Des Cartes ad celeberrimum virum D. Gisbertum Voetium ... [with a special half-title and separate paging,] 88 p. [First published as: Renati Des-Cartes, meditationes de prima philosophia, in qua Dei existentia et animae immortalitas demonstratur. Parisiis, Apud Michaelem Soly, 1641.]

ENGLISH: *Six Metaphysical Meditations; Wherein it is Proved That There is a God. And That Man's Mind is Really Distinct from His Body.* Written originally in Latin by Renatus Des-cartes. Hereunto are added the objections made against these meditations. By Thomas Hobbes of Malmsbury. With the authors answers. All faithfully translated into English, with a short account of Des-cartes's Life. By William Molyneux ... London: Printed by B.G. for Benj. Tooke ... 1680. 8 p.l.,160 p. 17 1/2 cm.

3. Descartes, René (1596-1650) *Les passions de l'ame.* Par René Des Cartes. A Paris, Chez Henry LeGras ... M.DC.XL.IX ... [1649.] 24 p.l.,286 p. 16 1/2 cm.

ENGLISH: *The Passions of the Soule in Three Books. The First, Treating of the Passions in Generall, and Occasionally of the Whole Nature of Man. The Second, of the Number, and Order of the Passions, and the Explication of the Six Primitive Ones. The Third, of Particular Passions.* By R. des Cartes. And translated out of French into English. London, Printed for A.C. and are to be sold by J. Martin, and J. Ridley ... 1650. 15 p.l.,173 p. 14cm.

4. Malebranche, Nicolas (1638-1715) *Father Malebranche's Treatise Concerning The Search after Truth. The Whole Work Compleat. To which is Added The Author's Treatise of Nature, and Grace. Being A Consequence of the Principles Contain'd in the Search: Together with His Answer to the Animadversions upon the First Volume: His Defense against the Accusations of Mr. De la Ville, etc. Relating to the same Subject.* All translated by T. Taylor, M.A. ... Oxford, Printed by L. Lichfield, for Thomas Bennet Bookseller, ... London. M.DC.XCIV. [1694]. 6 p.l.,172(i.e.,176),[4],10,203,[1],42 p. diagrams. 33 1/2 cm. [First published in French as De la recherche de la vérité, o□ l'on traitte de la nature de l'esprit de l'homme, & de l'usage qu'il en doit faire pour éviter l'erreur dans les sciences. Ã Paris, Chez André Pralard, 1674-1675. 2 vols.]

5. Spinoza, Benedictus de [Spinoza, Baruch] (1632-1677) *B. d. S. Opera posthuma, quorum series post praefationem exhibetur.* ... M.DC.LXXVII. [Amstelodami, J. Rieuwertsz, 1677.] 20 p.l.,614,[34],112,[8] p. diagrams. 21 1/2 x 17 cm.

ENGLISH: *Benedict de Spinoza; His Life, Correspondence, and Ethics*. By R. Willis, M.D. ... London: Trübner & Co., ... 1870. xliv,[2],647,[1] p. 23 cm.

6. La Mettrie, Julien Offray de (1709-1751) *L'homme machine* ... Ã Leyde, De l'Imp. d'Elie Luzac, Fils, MDCCXLVIII. [1748]. 10 p.l.,109,[1] p. 14 1/2 cm.
[There are three French editions of 1748. The "W' edition has 108 pages and is exceptionally rare. The "X" edition has 109 pages with errors of "W" corrected; it is the standard edition. The "Y' edition has 148 pages, with additional corrections possibly by La Mettrie, but is possibly a pirated edition.]

ENGLISH: Man a Machine. Translated from the French of the Marquiss D'Argens. London: Printed for W. Owen, 1749. 87 p.12mo.

7. Cabanis, Pierre Jean Georges (1757-1808) *Rapports du physique et du moral de l'homme*, par P.J.G. Cabanis ... De l'imprimerie de Crapelet. A Paris, Chez

Crapart, Caille et Ravier, ... an X -- 1802. 2 vols. xliv,484; [4],624 p. 20 cm. [Portions of the Rapports first appeared in the Mèmoires des sciences et arts: sciences morales et politiques. Paris ... Baudouin, imprimeur de l'Institut national, 1798,1799,1801,1803.]

ENGLISH: *On the Relation Between the Physical and Moral Aspects of Man[.]* by Pierre-Jean-George Cabanis[.] Edited by George Mora, with introductions by Sergio Moravia and George Mora[.] Translated by Margaret Duggan Saidi [from the second edition, reviewed, corrected and enlarged by the author, 1805] ... The Johns Hopkins University Press[,] Baltimore and London[.] [1981]. 2 vols. xci,[i],357,[1]; [4],363-796 p. port. 25 cm.

8. Hodgson, Shadworth Holloway (1832-1912) *The Theory of Practice[.] An Ethical Enquiry in Two Books[.]* By Shadworth H. Hodgson. ... London: Longmans, Green, Reader, and Dyer. 1870. 2 vols. xii,566; viii,501,[1] p.
22 1/2 cm.

9. Carpenter, William Benjamin (1813-1885) *Principles of Mental Physiology, with their Applications to the Training and Discipline of the Mind, and the Study of its Morbid Conditions.* By William B. Carpenter ... London, Henry S. King & Co., ... 1874. xxi,[1],737,[1] p. illus. 20 1/2 cm.

10. Lewes, George Henry (1817-1878) *The Physical Basis of Mind. With Illustrations. Being the Second Series of Problems of Life and Mind.* By George Henry Lewes. London: Trübner & Co., ...1877. xiv,[2],493,[3] p. illus. 23 cm.

11. Prince, Morton (1854-1929) *The Nature of Mind and Human Automatism.* By Morton Prince, M.D., ...Philadelphia: J.B. Lippincott Company. ...1885. x,173,[1] p. 20 cm.

12. Gall, Franz Josef (1758-1828) and Spurzheim, Johann Gaspar [Spurzheim, Johann Kaspar; Spurzheim, Johann Christoph] (1776- 1832) *Anatomie et physiologie du système nerveux en général, et du cerveau en particulier, avec des observations sur la possibilité de reconnoître plusieurs dispositions intellectuelles et morales de l'homme et des animaux, par la configuration de leurs têtes;* par F.J. Gall et G. Spurzheim. Premier -- [quatrième] volume ... Paris, F. Schoell, ... 1810-1819. 4 vols. + atlas. 2 p.l.,lix,[1],352; 2 p.l.,466,[2]; 4 p.l.,xxxiii,[1],372; 3 p.l.,404 p.; atlas: 1 p.l., 100 plates (1fold). 31 cm., atlas: 55 cm.

13. Flourens, Marie-Jean-Pierre (1794-1867) Recherches expérimentales sur les propriétés et les fonctions du système nerveux, dans les animaux vertébrés; par P. Flourens. A Paris, Chez Crevot[,] ... 1824. 2 p.l.,xxvi,331,[3] p. 20 cm.

ENGLISH: Flourens, Pierre. Investigations of the properties and the functions of the various parts which compose the cerebral mass. [Pp. 85-122]. In: *Some Papers on the Cerebral Cortex[.]* Translated from the French and German by Gerhardt von Bonin[.] ... Charles C. Thomas ... Publisher[,] Springfield, Illinois ... [1960.] Pp. 3-21.

14. Bain, Alexander (1818-1903) *The Senses and the Intellect.* By Alexander Bain ... London: John W. Parker and Son ... 1855. xxxi,[1],614 p. illus. 22 1/2 cm.

The Emotions and the Will. By Alexander Bain ... London: John W. Parker and Son ... 1859. xxviii,649,[1] p. 22 ½ cm.

15. Spencer, Herbert (1820-1903) *The Principles of Psychology.* By Herbert Spencer ... London: Longman, Brown, Green, and Longmans. 1855. viii,620 p. 22 cm.

16. Broca, Pierre Paul (1824-1880) Remarques sur le siége de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole), par M. Paul

Broca, ... *Bulletins de la société anatomique de Paris,* 1861, année 36, 2ème serie, tome 6, 330-357.

ENGLISH: Broca, Paul. Remarks on the seat of the faculty of articulate language, followed by an observation of aphemia. In: *Some Papers on the Cerebral Cortex[.]* Translated from the French and German by Gerhardt von Bonin[.] ... Charles C. Thomas ... Publisher[,] Springfield, Illinois ... [1960.] Pp. 49-72.

17. Jackson, John Hughlings (1835-1911) *Clinical and Physiological Researches on the Nervous System. (Reprints.) No. 1. -- On the Localisation of Movements in the Brain.* By J. Hughlings Jackson, ... [Reprinted from the "Lancet," 1873.] J. and A. Churchill ... [1875.] 2 p.l.,xlviii,37,[1] p. 21 1/2 cm.

18. Ferrier, David (1843-1928) *The Functions of the Brain[.]* By David Ferrier, ... London[,] Smith, Elder, & Co., ... 1876[.] xv,[1],323,[1] p. 22 cm.

19. Mesmer, Franz Anton (1734-1815) *Mémoire sur la découverte du magnétisme animal;* par M. Mesmer, ... A Geneve; Et se trouve A Paris, Chez P. Fr. Didot le jeune, Libraire-Imprimeur de Monsieur, ... M.DCC.LXXIX. [1779]. 2 p. l.,vi,85,[3] p. 17 cm.

ENGLISH: Mesmerism[.] by Doctor Mesmer (1779)[.] *Being the first translation of Mesmer's historic Mémoire sur la découverte du magnétisme animal to appear in English[.]* With an Introductory Monograph by Gilbert Frankau (1948)[.] Macdonald : London[.] [1948.] frontis,63,[1] p. illus., ports. 18 1/2 cm.

20. Puységur, Armand-Marie-Jacques de Chastenet, Marquis de (1751-1825) *Mémoires pour servir a l'histoire et a l'établissement du magnétisme animal. ...* [Paris,]1784. 3 p. l.,[7]-170,[1] p. 20 cm.

21. Braid, James (ca.1795-1860) *Neurypnology; or, the Rationale of Nervous Sleep, Considered in Relation with Animal Magnetism. Illustrated by Numerous Cases of Its Successful Application in the Relief and Cure of Disease.* By James Braid, ... London: John Churchill, ... Adam & Charles Black, Edinburgh. 1843. xxii,265,[1] p. 17 1/2 cm.

22. Liébeault, Ambroise Auguste (1823-1904) *Du sommeil et des états analogues considérés surtout au point de vue de l'action du moral sur le physique[,]* par A.-A. Liébeault ... Paris[,] Victor Masson et fils ... ; Nancy[,] Nicolas Grosjean, ... 1866[.] 535,[1] p. 22 cm.

23. Charcot, Jean-Martin (1825-1893) *Leçons sur les maladies du système nerveux faites à la Salpétriere[.]* Par J.-M. Charcot ... Recueillies et publiées par [Desiré Maglivre] Bourneville[.] ... Paris[:] Adrien Delahaye, Libraire-Éditeur[,] 1872- 1873. [vi],368 p., plates. 22 1/2 cm. [Originally issued in 4 parts, paginated as: [iv],96; 97-192, 193-256, [viii],257-368 p. A second volume, also in 4 parts, was issued between 1873 and 1877; and a third volume appeared in 1883 under the editorship of Babinski, Bernard, Féré, Guinon, Marie et Gilles de la Tourette].

ENGLISH: *Lectures on the Diseases of the Nervous System. Delivered at La Salpétrière,* by J.M. Charcot, ... Translated by George Sigerson, M.D., ... London: The New Sydenham Society. MDCCCLXXVII [1877.] xiii,[3],325,[1] p., plates, 22 1/2 cm. [The second and third volumes appeared in translation in 1881 and 1889.]

24. Bernheim, Hippolyte (1840-1919) *De la suggestion dans l'état hypnotique et dans l'état de veille[.]* par Le Dr. Bernheim ... Paris[,] Octave Doin, ... 1884[.] 110 p. 24 1/2 cm.

ENGLISH: *Suggestive Therapeutics[.] A Treatise on the Nature and Uses of Hypnotism[.]* By H. Bernheim, M.D. ... Translated from the second and revised French edition by Christian A. Herter, M.D. ... New York & London[,] G.P. Putnam's Sons ... 1889[.] xvi,420 p. diagrs., facsims. 23 1/2 cm.

25. Janet, Pierre-Marie-Félix (1859-1947) *L'automatisme psychologique[;] essai de psychologie expérimentale sur les formes inférieures de l'activité humaine[,]* par Pierre Janet ... Paris[,] Ancienne Librairie Germer Baillière et Cie[,] Félix Alcan, Éditeur ... 1889[.] 4 p.l.,496 p. diagrs. 22 cm.

26. Breuer, Josef (1842-1925) and Freud, Sigmund (1856-1939) Ueber den psychischen Mechanismus hysterische Phänomene. (Vorläufige mittheilung.) Von Dr. Josef Breuer und Dr. Sigm. Freud ... *Neurologische Centralblatt,* 1893, 12te jahrgang [Leipzig: Verlag von Veit & Comp.], 4-10, 43-47.

ENGLISH: ... *Studies in Hysteria,* by Dr. Joseph Breuer and Dr. Sigmund Freud; authorized translation with an introduction by A.A. Brill ... New York and Washington, Nervous and Mental Disease Publishing Company, 1936. ix,241 p. 23 1/2 cm. [Nervous and Mental Disease Monograph Series. No. 61 -- a translation of Studien über Hysterie von Dr. Jos. Breuer und Dr. Sigm. Freud[.] Leipzig und Wien. Franz Deuticke 1895, which supplemented the original paper with additional material].

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

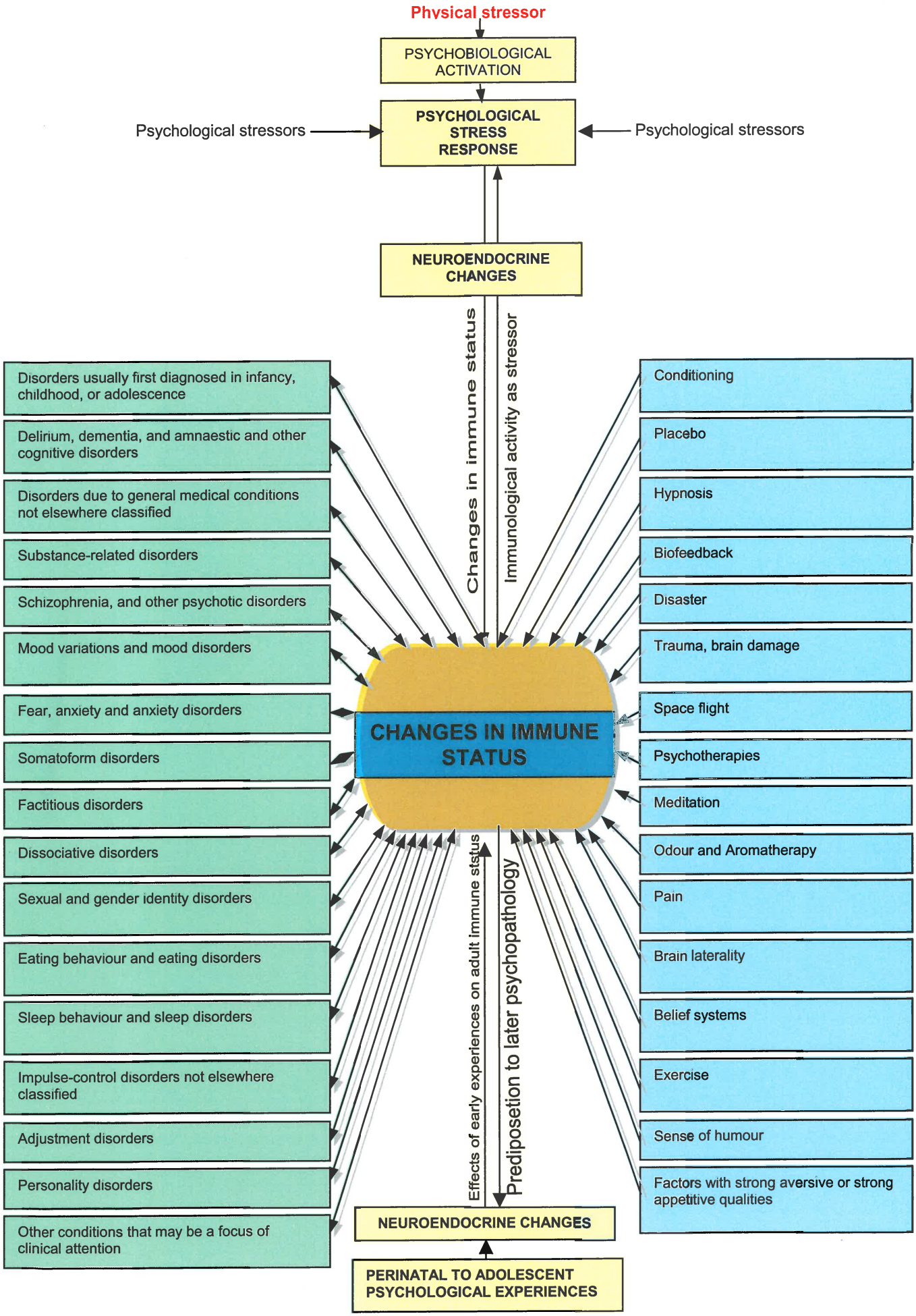

Figure 2.1: Conditions and behaviours with proven alterations in immune status

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.

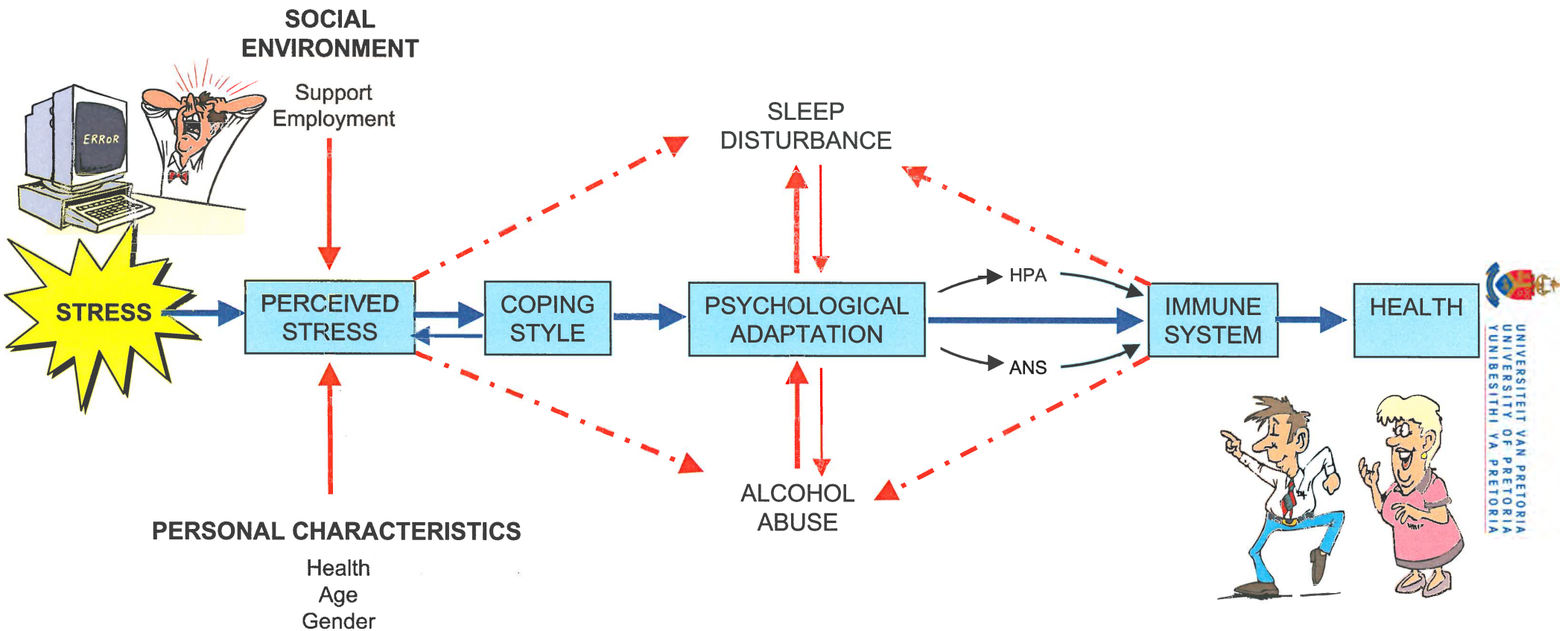

Figure 2.2: Biopsychosocial model of the relationship between stress and health.
(HPA = hypothalamic-pituitary-adrenocortical axis; ANS = autoimmune nervous system.
Adapted from (198))

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.

References

1. Pavlov IP. Lectures on conditioned reflexes. New York: Liveright, 1928.

2. Metal'nikov S, Chorine V. Role des reflexes conditionnels dans I'mmunite. Annales de I'Institute Pasteur, Paris 1926;40: 893-900.

3. Metal'nikov S, Chorine V. Role des reflexes condtionnels dans la formation des anticorps. Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales 1928;102:133-134.

4. Mackenzie, JN. The production of the so-called "rose cold" by means of an artificial rose. American Journal of Medical Science 1896; 91: 45-57.

5. Psychoneuroimmunology . R Ader (ed), (1st ed), Academic Press, New York, 1981.

6. Ader A, Cohen N. The influence of conditioning on immune responses. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology. (2nd ed). Academic Press, Inc., San Diego, California, pp611-646.

7. Klosterhalfen W, Klosterhalfen S. Conditioning of pharmacological effects in autoimmune diseases. In: Alan J Husband (ed). Behavior and Immunity. CRC Press Inc., London, 1992.

8. Dyck DG, Greenberg AH. Immunopharmacological tolerance as a conditioned response: Dissecting the brain-immune pathways. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (2nd ed). Academic Press Inc, San Diego, California, 1991, pp663-684.

9. Bull DF, Brown R, King MG, Husband AJ and Pfister HP. Thermoregulation: Modulation of body temperature through behavioral conditioning. In: Alan J Husband (ed). Behaviour and Immunity. CRC Press Inc., London, 1992, pp85-97

10. Gauci M, Bull DF, Schedlowski M, Husband AJ, King MG. (1992) Antilymphocyte serum and lithium chloride as a compound unconditioned stimulus for immunomodulation. In: Alan J Husband (ed). Behaviour and Immunity. CRC Press Inc., London, 1992, 99-105.

11. Shibata H, Fujiwara R, Iwamoto M, Matsuoka H, Yokoyama MM. Restoration of immune function by olfactory stimulation. In: H-S Schmoll, U Tewes, NP Plotnikoff (eds). Psychoneuroimmunology. Interactions between nervous system, behaviour, endocrine and immune system. Hogrefe & Huber Publishers Lewiston, NY, 1992, pp161-171.

12. Arora RB, Taneja V, Sharma RC. Anti-inflammatory studies on a crystalline steroid isolate from Commiphora mukul. Indian J Med Res 1973;60:929-931.

13. Ader R, Grota LJ, Moynihan JA, Cohen N. Behavioural adaptations in autoimmune disease-susceptible mice. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology, (2nd ed). Academic Press, Inc. San Diego, California, 1991.

14. Gauci M, Husband AJ, King MG. Conditioned allergic rhinitis: A model for central nervous system and immune system interaction in IgE-mediated allergic reactions. In: Alan J Husband (ed). Behaviour and Immunity. CRC Press Inc., London, 1992, pp71-83.

15. Ikemi Y, Nakagawa S. A psychosomatic study of contagious dermatitis. Kyushu Journal of Medicine/Science 1962;13:335-350.

16. Ader R, Cohen N. Conditioning and immunity. In: R Ader, DL Felten, N Cohen. Psychoneuroimmunology, Vol 2, 3rd ed. Academic Press, San Diego, 2001, pp3-34.

17. Ker AME, Viljoen M. The role of placebo and the placebo response in clinical research. The Medicine Journal 2000;42(8):31-38.

18. Plotnikoff N, Murgo A, Faith R, Wybran J (eds). Stress and Immunity. CRC Press, London. 1991.

19. Nicol L. L'epopee pastorienne et la medecine veterinaire. Garches France 1974, pp 197-211.

20. Asterita MF. The physiology of stress. Human Science Press, Inc., New York, 1985.

21. Monjan AA, Collector MI. Stress-induced modulation of the immune response. Science 1977;196:307-308.

22. Toge T, Hirai T, Tikiyama W, Hattori T.Effects of surgical stress on natural killer cell activity, proliferative response of spleen cells and cytostatic activity of lung macrophages in rats. Gann 1981;72:790-794.

23. Odio M, Brodish A, Ricardo MJ. Effects on immune responses by chronic stress are modulated by aging. Brain Behav Immun 1987;1:204-215.

24. Laudenslager ML, Ryan SM, Drugen RL, Hyson RL, Maier SF. (1983). Coping and immunosuppression: Inescapable but not escapable shock suppresses lymphocyte proliferation. Science 1983;221:568-570.

25. Shavit Y, Ryan SM, Lewis JW, Laudenslager ML, Terman GW, Maier SF, Gale RP, Liebeskind JC. Inescapable but not escapable stress alters immune function. Physiologist 1983;26:A64.

26. Ackerman SH, Keller SE, Schleifer SJ, Shindledecker RD, Camerino M, Hofer MA, Weiner H, Stein M. Premature maternal separation and lymphocyte function. Brain Behav Immun 1998;2:161-165.

27. Michaut R.J, DeChambre R P, Doumerc S, Lesourd B, Devillechabrolle A, Moulias R. Influence of early maternal deprivation on adult humoral immune response in mice. Physiol Behav 1981;26:189-191.

28. Fleshner M, Laudenslager ML, Simons L, Maier SF. Reduced serum antibodies associated with social defeat in rats. Physiol Behav 1989;45:118.

29. Bohus B, Koolhaas JM, Heijnen CJ, Ballieux RE, De Leij L, Kamstra A, De Boer O, Van Dijken H. Psychosocial enviroment and the immune system. In: W. Schonpflug (Ed), Bericht uber den 36 Kongress der Deutschen Gesellschaft fur Psychologie in Berlin, Gottingen: Hogrefe. 1989, pp 82-93.

30. Amkraut A, Solomon GF. Stress and murine sarcoma virus (Moloney)-induced tumors. Cancer Res 1972;32:1428-1433.

31. Temoshok L, Peeke HVS, Mehard CW, Axelsson K, Sweet DM. Stress- behavior interactions in hamster tumor growth. Ann NY Acad Sci 1987;496:501-509.

32. Bohus B, Koolhaas JM. Psychoimmunology of social factors in rodents and other subprimate vertebrates. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (2nd ed), Academic Press Inc., San Diego, Calfornia, 1991.

33. Edwards EA, Dean L.M. Effects of crowding of mice on humoral antibody formation and protection to lethal antigenic challenge. Psychosom Med 1977;39:19-24.

34. Binkhorst GJ, Henricks PA.J, v d Ing TSGAM, Hajer R, Nijkamp FP. The effect of stress on host defence system and on lung damage on calves experimentally infected with *Pasteurella haemolytica* Type A I. J Vet Med Ser A 1990;37: S25-S36.

35. Anderson N.V, Yoanes VD, Vestweber JG, King CA, Klemm RD, Kennedy GA. The effects of stressful exercise on leukocytes in cattle with experimental *Pneumonic pasteurellosis*. Vet Res Commun 1991;15:189-204.

36. Gross WB. Effect of a range of social stress severity on *Escherichia coli* challenge infection. Am J Vet Res 1984;452074-2076.

37. Ilback NG, Friman G, Beisel WR, Johnson AJ, Berendt RF. Modifying effects of exercise on clinical course and biochemical response of the myocardium in influenza and tularemia in mice. Infect Immun 1984;45:178-183.

38. Cole NA, Camp TH, Rowe LD Jr, Stevenson DG, Hutcheson D.P. Effect of transport on feeder calves. Am J Vet Res 1988;49:178-183.

39. Brown DH, Sheridan J, Pearl D, Zwilling BS. Regulation of myobacterial growth by the hypothalamus–pituitary-adrenal axis: Differential responses of *Myobacterium bovis* BCG-resistant and susceptible mice. Infect Immun 1993;61:4793-4800.

40. Dalal E, Medalia O, Harari O, Aroson M. Moderate stress protects female mice against bacterial infection of the bladder by eliciting uro-epithelial shedding. Infect Immun 1994;64:5505-5510.

41. Chang SS, Rasmussen AF. Stress induced suppression of interferon production in virus infected mice. Nature 1965;205:623-624.

42. Johnsson T, Rasmussen A.F. Emotional stress and susceptibility to poliomyelitis virus infection in mice. Arch Gesamte Virusforsch 1965;17;392-397.

43. Friedman SB, Glasgow LA, Ader R: Differential susceptiblity to a viral agent in mice housed alone or in groups. Psychosom Med 1970;32:285-299.

44. Gatmaitan BG, Chason JL, Lerner AM. Augmentation of the virulence of murine Coxsackie virus B-3 myocarditis by exercise. J Exp Med 1970;131:1121-1136.

45. Reyes MP, Lerner AM: Interferon and neutralizing antibody in sera of exercised mice with Coxsackie virus B-3 myocarditis. Proc Soc Exp Biol Med 1976;151:333-338.

46. Beard CW, Mitchell BW. Effects of environmental temperatures on the serologic responses of broiler chickens to inactivated and viable Newcastle disease vaccines. Avian Dis 1987;31:321-326.

47. Ben-Nathan D, Lustig S, Feuerstein G. The influence of cold or isolation stress on neuro-invasiveness and virulence of an attenuated variant of West Nile virus. Arch Virol 1989;109:1-10.

48. Bonneau RH, Sheridan JF, Feng N, Glaser R. Stress-induced suppression of *herpes simplex* virus (HSV)-specific cytotoxic T lymphocyte and natural killer cell activity and enhancement of acute pathogenesis following local HSV infection. Brain Behav Immun 1991;5:170-192.

49. Bonneau RH, Sheridan JF, Feng N, Glaser R. Stress-induced effects on cell mediated innate and adaptive memory components of the murine immune response to *herpes simplex* virus infection. Brain Behav Immun 1991;5:274-295.

50. Capitanio JP, Lerche NW. Psychosocial factors and disease progression in simian AIDS: A preliminary report. AIDS 1991;5:1103-1106.

51. Feng N, Pagniano R, Tovar CA, Bonneau RH, Glaser R, Sheridan JF. The effect of restraint stress on the kinetics, magnitude and isotype of the humoral immune response to influenza virus infection. Brain Behav Immun 1991;5:370-382.

52. Sheridan JF, Feng N, Bonneau RH, Allen CM, Huneycuts BS, Glaser R. Restraint stress differentially affects anti-viral cellular and humoral immune response in mice. J Neuroimmunol 1991;1:245-255.

53. Bonneau RH, Sheridan JF, Feng N, Glaser R. Stress-induced suppression of herpes simplex virus (HSV)-specific cytotoxic T lymphocyte and natural killer cell activity and enhancement of acute pathogenesis following local HSV infection Brain Behav Immun 1991;5:170-192.

54. Hermann G, Tovar CA, Beck FA, Allen C, Sheridan JF. Restraint stress differentially affects the pathogenesis of the experimental influenza viral infection in three inbred strains of mice. J Neuroimmunol 1993;47:83-94.

55. Hermann G, Tovar CA, Beck FM, Sheridan JF. Kinetics of glucocorticoid response to restraint stress and/or experimental influenza viral infection in two inbred strains of mice. J Neuroimmunol 1994;49:25-33.

56. Hamilton DR. Immunosuppresive effects of predator-induced stress in mice with acquired immunity to *Hymenolepis nana.* J Psychosom Res 1973;18:143-150.

57. El-Fakanhany AF, El-Ridi AM, Marii NE. Experimental toxoplasmosis: Effect of ambient temperature on lungs. J Egypt Soc Parasitol 1988;18:193-196.

58. Dantzer R, Mormede P. Psychoimmunology of stress. In: Brian E. Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. John Wiley and sons. New York, 1995, pp47-68.

59. Koolhaas JM, Bohus. Animal models of stress and immunity. In: Brian E. Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. John Wiley and sons. New York. 1995, pp69-84.

60. Denenberg VH. Commentary: Is maternal stimulation the mediator of the handling effect in infancy? Dev Psychobiol 1999;34(1):1-3.

61. Blecha F, and Kelly W. Effect of cold and weaning stressors on the antibody-mediated immune response of pigs. J Animal Sci 1981;53:439-445.

62. Michaut RJ, Deschambre RP, Doumerc S, Lesourd B, Devillechabrolle A, and Moulias R. Influence of early maternal deprivation on adult humoral immune response in mice. Physiol Behav 1981;26:189-191.

63. Ackerman SH, Keller SE, Scheifer SJ, Shindledecker RD, Camerino M, Hofer MA, Weiner H, Stein M. Premature maternal separation and lymphocyte function, Brain Behav Immun 1988;2:161-165.

64. Blecha F, Pollman DS, Nichols DA. Weaning pigs at an early age decreases cellular immunity, J Animal Sci 1983;56:396-399.

65. Gust DA, Gordon TP, Wilson M. E, Brodie AR, Ahmed-Ansari A, McClure HM. Removal from natal social group to peer housing affects cortisol levels and absolute numbers of T cell subsets in juvenile Rhesus monkeys. Brain Behav Immun 1992;6:189-199.

66. Ader R, Friedman SB. Differential early experiences and susceptibility to transplanted tumor in the rat. J Comp Physiol Psychol 1965;59:362-364.

67. Sandi C, Caston N, Vitiello S, Neveu PJ, Mormede P. Different responsiveness of spleen lymphocytes from two lines of psychogenetically selected rats (Roman high and low avoidance) J Neuroimmunol 1991;31:27-33.

68. Ingram DK, Corfman TP. An overview of neurobiological comparisons in mouse strains. Neurosci Biobehav Rev 1980;4:421-435.

69. Lyte M, Nelson SG. Baissa A. Examination of the neuroendocrine basis for the social conflict-induced enhancement of immunity in mice. Physiol Behavior 1990;48:685-690.

70. Temeshok L. On attempting to articulate the bio-psychosocial model: Psychological-psychophysiological homeostasis. In: HS. Friedman (ed). Personality and Disease, Wiley, New York. 1990, pp203-225.

71. Bohus B, Benus RF, Fokkema DS, Koolhaas JM, Nyakas C, Van Oortmerssen GA, Prins AJA, De Ruiter AJH, Scheurink AJW, Steffens AB. Neuroendocrine states and behavioral and physiological stress responses. In: ER. De Kloet, VM Wiegnant, D De Wied (eds). Progress in Brain Research (72nd Ed), Elsevier, Amsterdam, 1987, pp.57-70.

72. Benus RF, Bohus B, Koolhaas JM, Van Oortmerssen G.A. Heritable variation in aggression as a reflection of individual coping strategies. Experientia 1991; 47:1008-19.

73. Driscoll P, Demek J, D'Angio M, Claustre Y, Scatton B. Agenetically-based model for divergent stress responses: Behavioral, neurochemical and hormonal aspects. In: V Pliska and G Stranzinger (eds). Farm Animals in Biomedical Research (5th ed). Verlag Paul Parey, Hamburg. 1990, pp. 97-107.

74. McMillan FD. Influence of mental states on somatic health in animals. JAVMA 1999;214;1221-1225.

75. Koolhaas JM, Bohus B. Animal models in stress and immunity In: Brian E Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. John Wiley and Sons, Chichester, UK, 1995, p74.

76. Bondi M, Zannino G. Psychological stress, neuroimmunomodulation and susceptability to infectious diseases in animals and man: a review. Psychother Psychosom 1997;66:3-26.

77. Bondi M, Pancheri P. Clinical research studies in psychoimmunology. In: Brian E Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. John Wiley and Sons, Chichester, UK, 1995, pp85-111.

78. Dunn AJ. Infection as a stressor: A cytokine-mediated activation of the hypothalamo-pituitary-adrenal axis. Ciba Found Symp 1993;172:226-242.

79. Dunn AJ, Wan J, Ando T. Effects of cytokines on cerebral transmission: Comparison with the effects of stress. In: R Dantzer, EE Wollman, R Yirmiya (eds). Cytokines, stress and depression. Ad Exp Med Biol (vol 461). Kluwer Academic/Plenum Publishers, New York. 1999, pp117-128.

80. Jefferies WM. Cortisol and immunity. Med Hypoth 1991;34:198-208.

81. Cohen S, Williamson GM. Stress and infectious disease in humans. Psychol Bull 1991;109:5-24.

82. Fried I, Wilson CL, MacDonald KA, Behnke EJ. Electric current stimulates laughter. Nature 1998;391:650.

83. Berk LS, Tan SA, Napier BJ, Lee JW, Hubbard RW, Lewis JE, Eby WC. Neuroendocrine and stress hormone changes during mirthful laughter. Am J Med Sci 1989;298:390-396.

84. Dillon KM, Minchoff B, Baker KH. Positive emotional states and enhancement of the immune system. Int J Psychiatry Med 1985;15:13-18.

85. Gradner JW, Lyon JL. Cancer in Utah Mormone men by church activity level. Am J Epidemiol 1982; 116:243-257.

86. Berkel J, DeWaard F. Mortality pattern and life expectancy of Seventh Day Adventists in the Netherlands. Int J Epidemiol 1983;12:455-459.

87. Kark JD, Carmel S, Sinnreich R, Goldberger N, Friedlander Y. Psychosocial factors among members of secular and religious kibbutzim. Isr Med Sci 1996;32:185-194.

88. Koenig HG, Cohen HJ, George LK, Hays JC, Larson DB, Blazer DG. Int J Psychiatry Med 1997;5:131-144.

89. Orme-Johnson D. Medical care utilization and the transcendental medical program. Psychosom Med 1983;49:493-507.

90. Diagnostic and statistical manual of mental disorders. IV edition. American Psychiatric Association, Washington DC, 1995.

91. Mittleman BB, Castellanos FX, Jacobsen LK, Rapoport JL, Swedo SE, Shearer GM. Cerebrospinal fluid cytokines in pediatric neuropsychiatric disease. J Immunol 1997;159(6):2994-2999.

92. Birmaher B, Rabin BS, Garcia MR, Jain U, Whiteside TL, Williamson DE, al-Shabbout M, Nelson BC, Dahl RE, Ryan ND. Cellular immunity in depressed, conduct disorder, and normal adolescents: role of adverse life events. J Am Acad Child Adolesc Psychiatry 1994; 33(5):671-678.

93. Kaplan BJ, Crawford SG. The GBG model: Is there more to consider than handedness? Brain Cogn 1994;26(2):291-299.

94. Sigurdardottir S, Myers SM, Woodworth JM, Raymond GV. Mental retardation and seizure disorder in Schimke's immuno-osseous dysplasia. Am J Med Gen 2000;90(4):294-298.

95. Van Gent T, Heijnen CJ, Treffers PD. Autism and the immune system. J Child Psychol Psychiatry 1997;38 (3);337-349.

96. Mosek A, Yust I, Treves TA, Vardinon N, Korczyn AD, Chapman J. Dementia and antiphospholipid antibodies. Dem Ger Cog Dis 2000; 11(1):36-38.

97. Xu XH, Feng Y, Zhang XH, Liu GZ, Peng DT, WEN SG, Guo H, Zhang H, Wang H, Jiang Y, Li BL. Vascular dementia, with special reference to its vascular and immunological events. Alz Dis Ass Dis 1999;13 Suppl 3:S179-191.

98. Cotter RL, Burke, WJ, Thomas VS, Potter JF, Zheng J, Gendelman HE. Insights into the neurodegenerative process of Alzheimers disease: a role for mononuclear phagocyte-associated inflammation and neurotoxicity. J Leuk Biol 1999;65(4):416-427.

99. Sharief MK, Green A, Dik JP, Gawler J, Thompson EJ. Heightened intrathecal release of proinflammatory cytokines in Creutzfeldt-Jakob disease. Neurology 1999;52(6):1289-1291.

100. Marx F, Blasko I, Pavelka M, Grubeck-Loebenstein B. The possible role of the immune system in Alzheimer's disease. Exp Geront 1998;33(7-8):871-881.

101. McGreer PL, McGreer EG. Glial cell reactions in neurodegenerative disease: pathophysiology and therapeutic interventions. Alz Dis Ass Dis 1998; 12 Supp l2;S1-6.

102. Schubert P, Rudolphi K. Interfering with the pathological activation of microglial cells and astrocytes in dementia. Alz Dis Ass Dis 1998; 12 Suppl 2;S21-28.

103. Schmidt S. S100B: Pathogenic and pathophysiological significance in neurology. Nervenarzt 1998;69(8):639-646.

104. Eikelenboom P, Rozemuller JM, van Muiswinkel FL. Inflammation and Alzheimers disease: relationships between pathogenic mechanisms and clinical expression. Exp Neurol 1998;154(1):89-98.

105. Singh VK. Neuroautoimmunity: pathogenic implication for Alzheimer's disease. Gerontology 1997;43(1-2);79-94.

106. Harold I Kaplan, Benjamin J Sadock (eds). Comprehensive Textbook of Psychiatry, 6th Ed., Williams and Wilkins, Baltimore, USA, 1995, p716.

107. Hesselgresser J, Horuk R. Chemokine and chemokine receptor expression in the central nervous system. J Neuroviriol 1999;5(1):13-26.

108. Panzer A, Viljoen M. Psychoimmunology and HIV/AIDS. SAMJ 2002;92(1):31-33.

109. Ironson GH, Woods TE, Antoni MH. HIV disease: Psychological well-being and immunity. In: Alan Watkins (ed). Mind-body medicine. A clinicians guide to psychoneuroimmunology. Churchill Livingstone, NY, 1997, pp118.

110. Ironson GH, Woods TE, Antoni MH. HIV disease: Psychological well-being and immunity. In: Alan Watkins (ed). Mind-body medicine. A clinicians guide to psychoneuroimmunology. Churchill Livingstone, New York, 1997, pp115.

111. Ironson GH, Woods TE, Antoni MH. HIV disease: Psychological well-being and immunity. In: Alan Watkins (ed). Mind-body medicine. A clinicians guide to psychoneuroimmunology. Churchill Livingstone, NY, 1997, pp119-125.

112. Scott E, Hickie I, Lovric K. Auto-immune disease in patients hospitalized with depressive disorders. In: Alan J Husband (ed). Psychoimmunology. CNS-immune interactions. CRC Press, Inc. London, 1993, p79.

113. Agius MA, Arnason BGW. Auto-immune neurological diseases and their potential relevance to psychiatric diseases. In: JM Gorman, RM Kerzner. Psychoimmunological Update. Progress in Psychiatry, No 35. American Psychiatric Press, Inc., Washington DC, 1991, pp 9-22.

114. Nisipeanu P, Korczyn AD. Psychological stress and multiple sclerosis. In: Brian E Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. Wiley and Sons, Chichester, UK, 1995, pp165-183.

115. Harold I Kaplan, Benjamin J Sadock (eds). Comprehensive Textbook of Psychiatry, 6th Ed., Williams and Wilkins, Baltimore, USA, 1995, p6110.

116. Harold I Kaplan, Benjamin J Sadock (eds). Comprehensive Textbook of Psychiatry, 6th Ed., Williams and Wilkins, Baltimore, USA, 1995, p725.

117. Nisipeanu P, Korczyn AD. Psychological stress and multiple sclerosis. In: Brian E Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. Wiley and Sons, Chichester, UK, 1995, pp171-176.

118. Archelos JJ, Hartung HP. The role of adhesion molecules in multiple sclerosis: biology, pathogenesis and therapeutic implication. Mol Med Today 1997;3(7):319-321.

119. Petter G, Haustein UF. Steven-Johnson syndrome with transition to toxic epidermal necrolysis after carbamazepine administration, heroin and alcohol abuse. Hautartzt 1999;50(12):884-888.

120. Soderberg LS, Immunomodulation by nitrite inhalants may predispose abusers to AIDS and Karposi's sarcoma. J Neuroimmunol 1998;83(1-2):157-161.

121. Muller N, Ackenheil M. The immune system and schizophrenia. In: Brian E Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. Wiley and Sons, Chichester, UK, 1995, pp137-164.

122. Ganguli R, Rabin DS. Decreased interleukin-2 synthesis and reduced T-suppressor cells in schizophrenic patients: evidence of autoimmunity. Ann Meeting Am Coll Neuropsychopharmacol ,1987, S. Juan , Puerto Rico.

123. Hornberg M, Arolt V, Kirchner H. Lymphokine production in patients with schizophrenia. 8th Spring meeting of the Gesellschaft fur Immunologie, 1989, Munchen (abstract).

124. Ganguli R, Rabin BS. Increased serum interleukin-2 receptor concentration in schizophrenics and brain damaged subjects. Arch Gen Psychiatry 1989;46:292

125. Rapoport MH, McAllister CG, Pickar D, Nelson DM, Paul SM. Elevated levels of soluble interleukin-2 receptors in schizophrenia. Arch Gen Psychiatry 1989;46:291-292.

126. Huang Y, Perrin LH, Miescher PA, Zubler RH. Correlation of T and B cell activities *in vitro* and serum interleukin-2 levels in systemic lupus erythematosis. J Immunol 1988;141:827-833.

127. Muller N, Ackenheil M. The immune system and schizophrenia. In: Brian E Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. Wiley and Sons, Chichester, UK, 1995, p151.

128. Muller N, Riedel M, Ackenheil M, Schwarz MJ. The role of immune function in schizophrenia: an overview. Eur Arch Psychiatry Clin Neurosci 1999;249 (suppl) 4:62-68.

129. Torrey EF, Torrey BB, Peterson MR. Seasonality of schizophrenic births in the United States. Arch Gen Psychiatry 1977;34;1065-1070.

130. Torrey EF. Prevalence studies of schizophrenia. Br J Psychiatry 1987;150 :598-608.

131. Callaghan E, Sham P, Takei N, Glover G, Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. Lancet 1991;1:1248-1250.

132. Tiwari IL, Terasaki PI. HLA and disease associations. Springer-Verlag, 1986.

133. Leonard BE. Stress and the immune system: Immunological aspects of depressive illness. In: Brian E Leonard and Klara Miller (eds). Stress, the immune system and psychiatry. Wiley and Sons, Chichester, UK, 1995, pp122.

134. Maes M, Smith R, Scharpe S. The monocyte T-lymphocyte hypothesis of major depression. Psychoneuroendocrinology 1995;20:111-116.

135. Maier SF, Watkins LR, Fleshner M. Psychoneuroimmunology: the interface between behavior, brain and immunity. Am J Psychol 1994;49:1004-1017.

136. Maier SF, Nguyen KT, Deak T, Milligan ED, Watkins LR. Stress, learned helplessness, and brain interleukin-1B. Adv Exp Med Biol 1999;461:235-249.

137. Irwin M. Immune correlates of depression. Adv Exp Med Biol 1999;461:1-24.

138. Leonard BE, Song C. Stress, Depression, and the role of cytokines. Adv Exp Med Biol 1999;461:251-265.

139. Licinio J, Wong M-L. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 1999;4:317-327.

140. Koh KB. Emotion and immunity. J Psychosom Res. 1998;45(2); 107-115.

141. Holden RJ, Pakula IS, Mooney PA. An immunological model connecting the pathogenesis of stress, depression and carcinoma. Med Hypothesis 1998; 51:309-314.

142. Plotnikoff NP, Faith RE, Murgo AJ, Good RA (eds). Cytokines. Stress and Immunity. CRC Press, NY, 1999.

143. Anisman H, Merali Z. Anhedonic and anxiogenic effects of cytokine exposure. Adv Exp Med Biol 1999;461:199-233.

144. Zavala F. Benzodiazepines, anxiety and immunity. Pharmacol Ther 997;75(3): 199-216.

145. Borella P, Bargellini A, Rovesti S, Pinelli M, Vivoli R, Solfrini V, Vivoli G. Emotional stability, anxiety, and natural killer activity under examination stress. Psychoneuroendocrinology 1999;24(6):613-627.

146. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). American Psychiatric Association, Washington DC, 1995, p445.

147. Panzer A, Viljoen M. Systemic candidiasis: some facts. SAMJ 2001;91(11):959-961.

148. Ford CV. Somatization and fashionable diagnoses: illness as a way of life. Scand J Work Environ Health.1997;23 Suppl 3:7-16.

149. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). American Psychiatric Association, Washington DC, 1995, p477-490.

150. Booth RJ, Ashbridge KR. Models of psycho-immune interplay and their impact on the directions of psychoimmunological research. In: Alan J Husband (ed). Psychoimmunology: CNS-immune interactions. CRC Press, Inc., Florida, 1993, p169.

151. Goodman RE. Understanding human sexuality, specifically homosexuality and the paraphilias in terms of chaos theory and fetal development. Med Hypotheses 1997;48(3): 37-43.

152. Haslett PA. Anticytokine approaches to the treatment of anorexia nervosa. Sem Oncol 1998;25(2Suppliment 6);53-57.

153. Mantovani G, Maccio A, Lai P, Massa E, Ghiani M, Santona MC. Cytokine activity in cancer related anorexia/cachexia: rol of megestrol acetate and medroxyprogesterone acetate. Sem Oncol 1998;(2Suppl 6):45-52.

154. Cook ME. Nutritional effects on vaccination. Adv Vet Med 1999;41:53-59.

155. Johnson RW. Immune and endocrine regulation of food intake in sick animals. Dom Animal End 1998;15(5):309-319.

156. Exton MS. Infection-induced anorexia: active host defense strategy. Appetite 1997;29(3);369-383.

157. Corcos M, Atger F, Levy-Soussan P, Avrameas S, Guilbert B, Cayol V, Jeammet P. Bulimia nervosa and autoimmunity. Psychiatry Res 1999;87(1):77-82.

158. Billiard M, Seignalet J. Extraordinary association between HLA-DR2 and narcolepsy. Lancet 1985;1:226-227.

159. Jiji T, Matsuki S, Naohara T. Extraordinary association between HLA-DR2 and narcolepsy. Lancet 1985;1227.

160. Neely S, Rosenberg R, Spire J-P. HLA antigens in narcolepsy. Neurology 1987;37:1858-1860.

161. De Montjoye BV, Wambergue D, Lecamp M, Larome K. Kleptomania and pyromania. Apropos of a case. Ann Med Psychol (Paris).1992;150(10):734-738.

161. Furusawa E. Furuya K. Terasawa K. Physiological changes in Pachinko players; beta-endorphin, catecholamines, immune system substances and heart rate. Appl Human Sci. 18(2):37-42, 1999.

162. Friedman HS, Personality and disease: Overview, review and preview. In: HS Friedman (ed). Personality and Disease. John Wiley and Sons, New York, 1990, pp3-13.

163. Friedman HS. The Self-Healing Personality, Henry Holt and Co, New York, 1991.

164. Friedman HS, Booth-Kewley S. The disease-prone personality: a meta-analytic view of the construct. Am Psychologist 1987; 42:539-555.

165. Morris T, Greer S. *A Type* C for cancer? Low trait anxiety in the pathogenesis of breast cancer. Cancer Detect Prev 1980;3 (Abstract No 102).

166. Temoshok L. Biopsychosocial studies on cutaneous malignant melanoma: Psychosocial factors associated with prognostic indicators, progression, psychophysiology, and tumor-host response. Soc Sci Med 1985;20:833-840.

167. Temoshok L. Personality, coping style, emotion and cancer: Toward an integrative model. Cancer Surveys 1987;6:837.

168. Temoshok L, Heller BW. On comparing oranges, apples and fruit salad: A methodological overview of medical outcome studies in psychosocial oncology. In: CL Cooper (ed), Psychosocial stress and cancer. Wiley and Son, Chichester UK, 1984.

169. McLelland D, Alexander C, Marks E. The need for power, stress, immune function, and illness among male prisoners. J Abn Psychology 1982;91:61-70.

170. Hardy JD, Smith TW. Cynical hostility and vulnerability to disease: Social support, life stress, and physiological response to conflict. Health Psychology 1988;7:447-460.

171. Smith TW, Frohm KD. What is so unhealthy about hostility? Construct validity and psychological correlates of the Cook and Medley Ho Scale. Health psychology 1985;4:503-520.

172. Schreier MF, Carver CS. Optimism, coping and health: Assessment and implications of generalized outcome expectancies. Health Psychology 1985;4:219-248.

173. Bandura A, Taylor CB, Williams SL, Melford IN, Barchas JD. Catecholamine secretion as a function of perceived self-efficacy. J Consult Clin Psychology 1985;53:406-414.

174. Eysenck HJ. Personality and stress as casual factors in cancer and coronary heart disease. In: MP Janisse (ed). Individual differences, stress and health psychology, Springer-Verlag, New York, 1988.

175. De Jongh MG, Van Sonderen E, Emmelkamp PMG. A comprehensive model of stress. The role of experienced stress and neuroticism in explaining the stress-distress relationship. Psychoter Psychosom 1999;68:290-298.

176. Suls J, Rittenhouse JD. Models of linkages between personality and disease In: Howard S Friedman (ed). Personality and disease John Wiley and Sons, New York, 1990.

178. Naidenova NN, Mishenev MV, Semke VA, Golovin OD, Vasil'eva OA. The characteristics of the interferon system parameters in typologically different groups of patients with borderline mental disorders during treatment. Zhevropatol Psikhiatr Im S S Korsakova. 94(5):74-6, 1994.

179. Vallee M, Mayo M, LeMoal M, Simon H, Maccari S. Prenatal stress induces high anxiety in adult offspring. Correlation with stress-induced corticosterone secretion. J Neurosci 1997;17:2626-2636.

180. Polterev T, Keshet GI, Kay G, Weinstock M. Role of experimental conditions in determining differences in exploratory behaviour of prenatally stressed rats. Dev Psychobiol 1996;29:453-462.

181. Clarke AS, Schneider ML. Prenatal stress has long-term effects on behavioural responses to stress in juvenile rhesus monkeys. Dev Psychobiol 1993;26:293-304.

182. Klein SL, Rager DR. Prenatal stress alters immune function in the offspring of rats. Dev Psychobiol 1995;28:321-326.

183. Coe CL, Lubach GR, Karaszewski JW, Erschler WB. Prenatal endocrine activation alters postnatal cellular immunity in infant monkeys. Brain Behav Immun 1996;10:221-234.

184. Kaupilla A, Hartikainen-Sorri AL, Koivisto M, Ryhanen P. Cell-mediated immunocompetence of children exposed *in utero* to short- or long-term glucocorticoids. Gynecol and Obstet Invest 1983;15:41-48

185. Del Rey A, Furukawa H, Monge-Arditi G, Kabierssch A, Voigt K-H. Alterations in the pituitary-adrenal axis of adult mice following neonatal exposure to interleukin-1. Brain Behav Immun 1996;10:235-248.

186. Roy A, Pickar D, Linnoila M, Doran AR, Paul SM. Cerebrospinal fluid monoamine and monoamine metabolite levels and the dexamethasone suppression test in depression: Relationship to life events. Arch Gen Psychiatry 1986;43:356-360.

187. Higley JD, Suomi SJ, Linnoila MA. A Longitudinal assessment of CSF monoamine metabolites and plasma cortisol concentration in young rhesus monkeys. Biol Psychiatry 1992;32:127-145.

188. Worlein JM, Laudenschlager ML. Effects of early rearing experiences and social interactions on immune function in nonhuman primates. In: R Ader, DL Felton, N Cohen (eds). Psychoneuroimmunology, 3rd ed, vol 2 . Academic Press, San Diego, 2001, pp73-86.

189. Catalani A Marinelli M, Scaccianoce S, Nicolai R, Muscolo LA, Porcu A, Koranyi L, Piazza PV, Angelussi L. Progeny of mothers drinking corticosterone during lactation has lower stress-induced corticosterone and better cognitive performance.Brain Res 1993;624:209-215.

190. Renoux G, Biziere K, Renoux M, Guillaumin JM, Degenne DA. A balanced brain asymmetry modulates T cell-mediated events. J Neuroimmunol 1983;5:227-238.

191. Neveu P, Taghzouti K, Dantzer R, Simon H, Le Moal M. Modulation of mitogen-induced lymphoproliferation by cerebral neocortex. Life Sciences 1986;38:1907-1913.

192. Blomgren HM, Blom V, Ullen H. Relation between the site of intracranial tumors and mitogenic responses of blood lymphocytes. Can Immunol and Immunother 1986;21:31-38.

193. Betancur C, Sandi C, Vitiello S, Borrell J, Guaza C, Neveu PJ. Activity of the hypothalmic-pituitary-adrenal axis in mice selected for left- or right-handedness. Brain res 1992;589:302-306.

194. McManus IC, Bryden MP, Bulman-Flemming MB. Handedness and autoimmune disease. Lancet 1993;341:891-892.

195. Booth RJ, Ashbridge KR. Models of psychoimmune interplay and their impact on the directions of psychoimmunological research. In: AJ Husband (ed). Psychoimmunology. CNS-immune interactions. CRC Press, Florida, 1993, pp163-177.

196. Gorman JM. Psychoimmunology: A Darwinian approach. In: JM Gorman, RM Kertzner (eds). Psychoimunology Update. Progress in psychiatry, Nr 35. American Psychiatric Press Inc, Washington DC, 1991, pp1-7.

197. Irwin MR, Stress and immune changes in humans: A biopsychosocial model. In: JM Gorman, RM Kertzner, Psychoimmunology Update. Progress In Psychiatry, Nr 35. American Psychiatric Press Inc., Washington DC, 1991, pp55-80.

198. Irwin MR, Stress and immune changes in humans: A biopsychosocial model. In: JM Gorman, RM Kertzner, Psychoimmunology Update. Progress in Psychiatry, Nr 35. American Psychiatric Press Inc., Washington DC, 1991, p56.

199. Turner-Cobbs JM, Sephton SE, Spiegel D. Psychosocial effects on immune function and disease progression in cancer: Human studies. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology 3rd ed, Vol 1. Academic Press, San Diego, 2001, pp565-582.

200. Kiecolt-Glaser JK, Glaser R. Psychoneuroimmunology: Can psychological interventions modulate immunity? J Consult Clin Psychol 1992;60:569-575.

CHAPTER 3

THE PSYCHONEUROLOGICAL INTERACTION IN TERMS OF THE CNA/SAM-AXIS

The aim of this chapter is to demonstrate the role of the central noradrenergic/sympatho-adrenomedullary axis (CNA/SAM-axis) in the behavioural functions and in behavioural disturbances. It also deals with the effects of psychological stress on the structure and functioning of the central noradrenergic system. It therefore represents the psychoneurological component of the psychoneuroimmunological interaction in terms of the CNA/SAM-axis. A wealth of experimental results gives credence to the importance of the CNA/SAM-axis in behaviour and the following paragraphs will provide some of the evidence, first in animals, and then in man. In an attempt to restrict the volume of work, more emphasis is placed on the psychoneurological interaction as evidenced from results and observations in humans, while animal studies are dealt with in a fairly concise way. The chapter is finally summarised in a heuristic model, depicting the central noradrenergic systems, their projections to other cerebral structures, their interactions with other neuroregulatory networks, their more specific cerebral effects and functions, as well as their relatedness to behavioural functions and psychiatric disorders.

CNA = central noradrenergic; SAM = sympathoadrenomedullary; NA = noradrenaline.

Introduction

The aim of Chapters 3 and 4 is to illustrate the psychoneuroimmunological interaction in terms of the first of the two major stress axes, i.e. the CNA/SAM axis. This chapter demonstrates the important role of the CNA/SAM-axis (central noradrenergic/sympathoadrenomedullary-axis) in behaviour and shows how emotional distress, as well as eustress, impacts on the structure and function of the central nervous system noradrenergic (CNA) neurons – with further long-term behavioural consequences. It therefore deals with the psychoneurological aspects of psychoneuroimmunology.

The layout of this chapter is as follows

3.1 The psychoneurological interaction in animals

3.2 The psychoneurological interaction in man

3.3 The bidirectional interaction between the psychological functions and the CNA/SAM-axis

3.4 Summary and heuristic model of the bidirectional interaction.

The distribution and projections of the CNA system, as well as its functions and interactions are shown in Figure 3.6. Figure 3.6 presents the final summary of the chapter and is given at the end of the chapter. However, a minimised version of it is also presented on the next page (Figure 3.1). There are two important reasons for showing the smaller scale version now and the larger scale version at the end. The first reason is that it is much easier to read the chapter having seen the overall distribution and functions of the system. The end of the chapter is, however, its rightful place and the larger, that is, easier to read version will thus be inserted there. The second reason is for the benefit of the reader not interested in the details of the interactions. The scheme on its own will, in such a case, provide enough information to verify the pervasiveness of the bidirectional influence between the noradrenergic system and the behavioural functions without having to read the fine details of the text.

Figure 3.1 is shown on the next page and its legend on the following page.

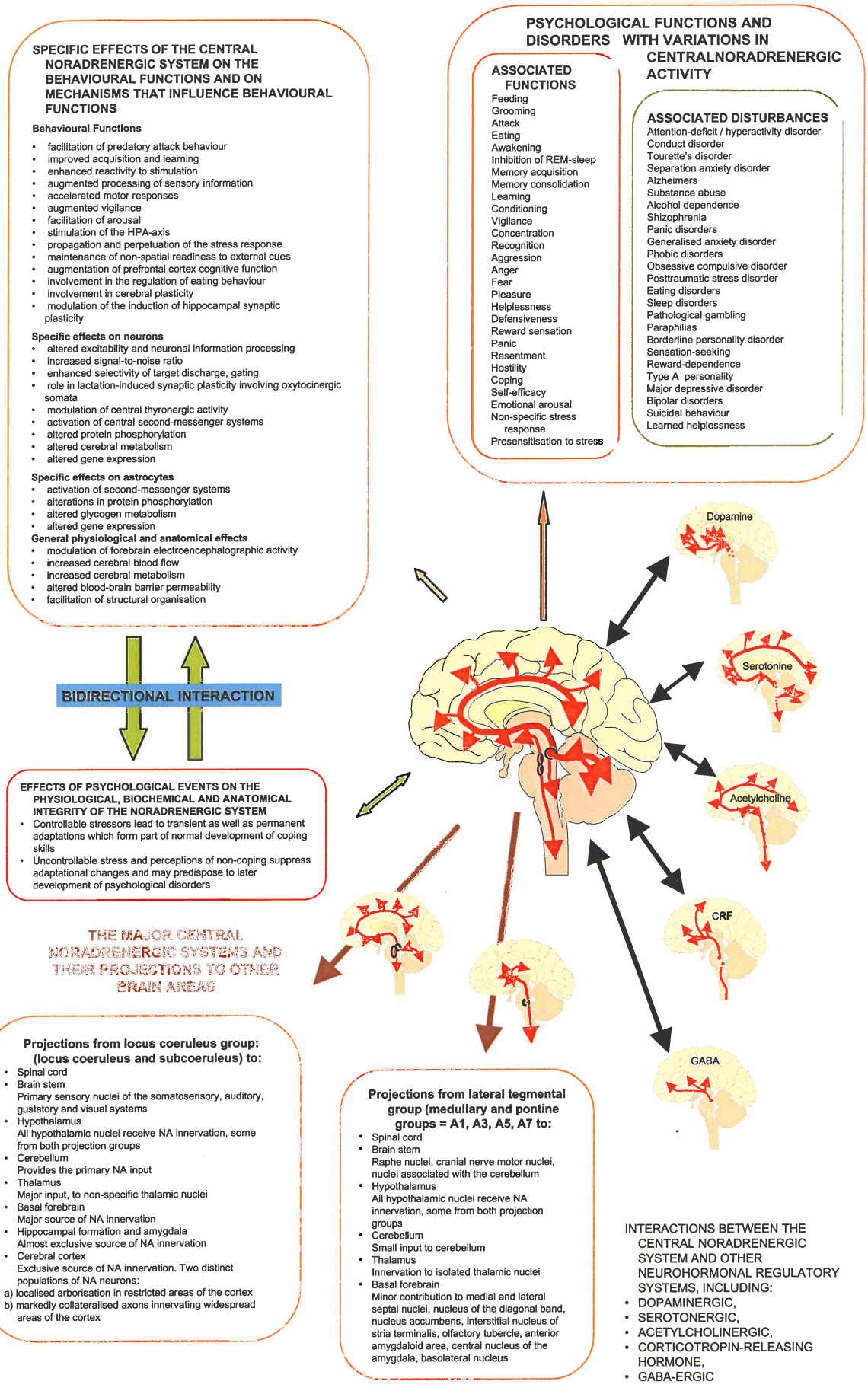

Figure 3.1: A heuristic model of the psychoneurological relationship in terms of the central noradrenergic system

Legend to Figure 3.1

Figure 3.1: A heuristic model of the psychoneurological relationship in terms of the central noradrenergic system.

[Figure 3.1 shows the structure-functional relationship of the CNA system. In the bottom left sector the two major divisions of the central noradrenergic (CNA) system with their projections are depicted. The top-left sector shows the specific effects of the noradrenergic influence. The top- right depicts the behavioural functions and disorders associated with variations in CNA activity and the bottom-right the interactions between the CNA system and other neuroendocrine modulatory systems. In the middle-left the bidirectional influence between structure and function is shown.]

3.1 The psychoneurological interaction in animals

Results from a multitude of publications confirm the existence of a link between the CNA/SAM-axis and the behavioural functions in animals. Studies on the association focus largely on adverse conditions and emotions, such as stress, fear, anxiety, and aggression. Hardly any animal studies have been performed in an attempt to examine the psychoneurological interaction during positive emotional states or to define the behavioural aspects in more discriminatory terms. This is partially due to problems involved in defining and categorising behavioural functions and dysfunctions in animals to the extent possible in man. Psychoneurological studies in animals are, however, of interest as the findings may sometimes be extrapolated to related clinical conditions in humans. Such studies are further relevant as they support the concept of a role for perception in the psychoneurological interaction. However, the most valuable contribution of animal studies is that certain processes and manoeuvres such as the measurement of central nervous system transmitters and activities, as well as direct neural manipulations, can be performed which are, for logistic and ethical reasons, not possible in man. Results from animal studies have opened a window into our understanding of the noradrenergic-related neurological mechanisms that underlie the behavioural functions and dysfunctions in man. Such noradrenaline-related mechanisms include processes involved in a) memory and memory impairment, b) fear, anxiety, aggression, stress, c) presensitisation to fear, to anxiety, to aggression and to stress, d) distortion of sensory and time perception, e) regulation of eat, sleep and drink, f) learned helplessness, g) traumatic recall/flashbacks of aversive events, as well as h) conditioning and failure to eliminate conditioned responses. It is easy to see how results from such experiments may be extrapolated to a number of psychopathological phenomena in man. A discourse on the feasible extrapolations is beyond the purpose of this writing. The aim of this section, which deals with the psychoneurological interaction in animals, is to provide the necessary evidence for this interaction in terms of the CNA/SAM-axis, and to resist the temptation to needless elaboration.

A major part of our knowledge on the psychoneurological interaction in animals is, as was previously mentioned, derived from experiments that involved activation of the central stress response. It is generally known that activation of the central stress response is almost without exception associated with an increase in central noradrenergic (CNA) activity. During periods of acute stress the CNA-activity can generally be measured as an increase in central noradrenaline release (CNA-release) and/or an increase in tyrosine hydroxylase production. However, continuous or excessive central noradrenaline release, as a result of chronic or inescapable stress, may lead to the situation where CNA-production is unable to keep up with CNA-release. It has been postulated that the resultant central noradrenergic depletion may be the cause of the chronic stress-induced behavioural alteration known as "learned helplessness" (1). The term "learned helplessness", as described by Seligman originated from experiments in which animals were subjected to uncontrollable shock. Learned helplessness in animals is by many considered to be a convincing laboratory model for depression in humans. This is based on the fact that the first six DSM-IV criteria for depression are seen in animals after uncontrollable, adverse experiences (2,3). Under such circumstances the stress-induced increase in noradrenergic neuron activity would be reflected as a decrease in CNA-content and/or an increase in MHPG, i.e., the major noradrenaline metabolite or even changes in the anatomical aspects of the CNA system. The effect of acute, as well as chronic stress on the various CNA parameters can be found in an excellent review by Bremner, *et al,* 1996 (4) that summarises the stress-induced alterations of CNA parameters in the cerebral cortex and in subcortical areas such as the hippocampus, the amygdala, the thalamus, and the hypothalamus.

Rapid activation of the central noradrenergic (CNA) system (locus coeruleus), as occurs during any episode of marked emotional arousal, is generally paralleled by simultaneous activation of the peripheral noradrenergic system, i.e., the SAM-axis (5). The synchronous activation of the locus coeruleus-CNA system and the peripheral SAM-axis would lead to the expression of central noradrenergically-induced behavioural alterations, and peripheral stress effects through the SAM-axis.

A considerable functional link exists between the peripheral part of the CNA/SAM-axis, i.e., the sympatho-adrenomedullary-axis (SAM-axis) and the behavioural functions. Due to the simultaneous activation of the locus coeruleus-central noradrenergic system and the SAM-axis, observations of hyperactivity of the latter are often equated with hyperactivity of the central noradrenergic (CNA) system. It is also known that wrong interpretations of some of the peripheral effects such as severe cardiac palpitations may have severe implications for the emotional stability. A discussion of alterations in the adrenomedullary noradrenaline:adrenaline ratio in major depressive states is deferred to the part dealing with the interaction in humans.

The peripheral so-called sympathetic effects are, as is well known, the result of direct stimulation by the sympathetic neurons, enhanced by the actions of circulating adrenomedullary hormones such as adrenaline and noradrenaline. The concomitant increase in activity in peripheral SAM-axis, at the time of emotions-associated CNA hyperactivity, involves neural structures such as the amygdala, descending projections from the locus coeruleus to the brainstem, as well as the nucleus paragigantocellularis (6,7). The effects of general activation of the peripheral sympatho-adrenomedullary system, (SAM-system) commonly known as the *alarm* or the *fight-or-fight* reaction, are summarised in Figure 3.2. Although it is by now common knowledge that these effects occur in man, the initial experimental results were all derived from animal experimentation (8).

The peripheral SAM-axis effects, as summarised in Figure 3.2, are determined by the type of adrenoceptor involved and the concentration of the transmitter substance. This is generally known and as such does not warrant further discussion at this point in time.

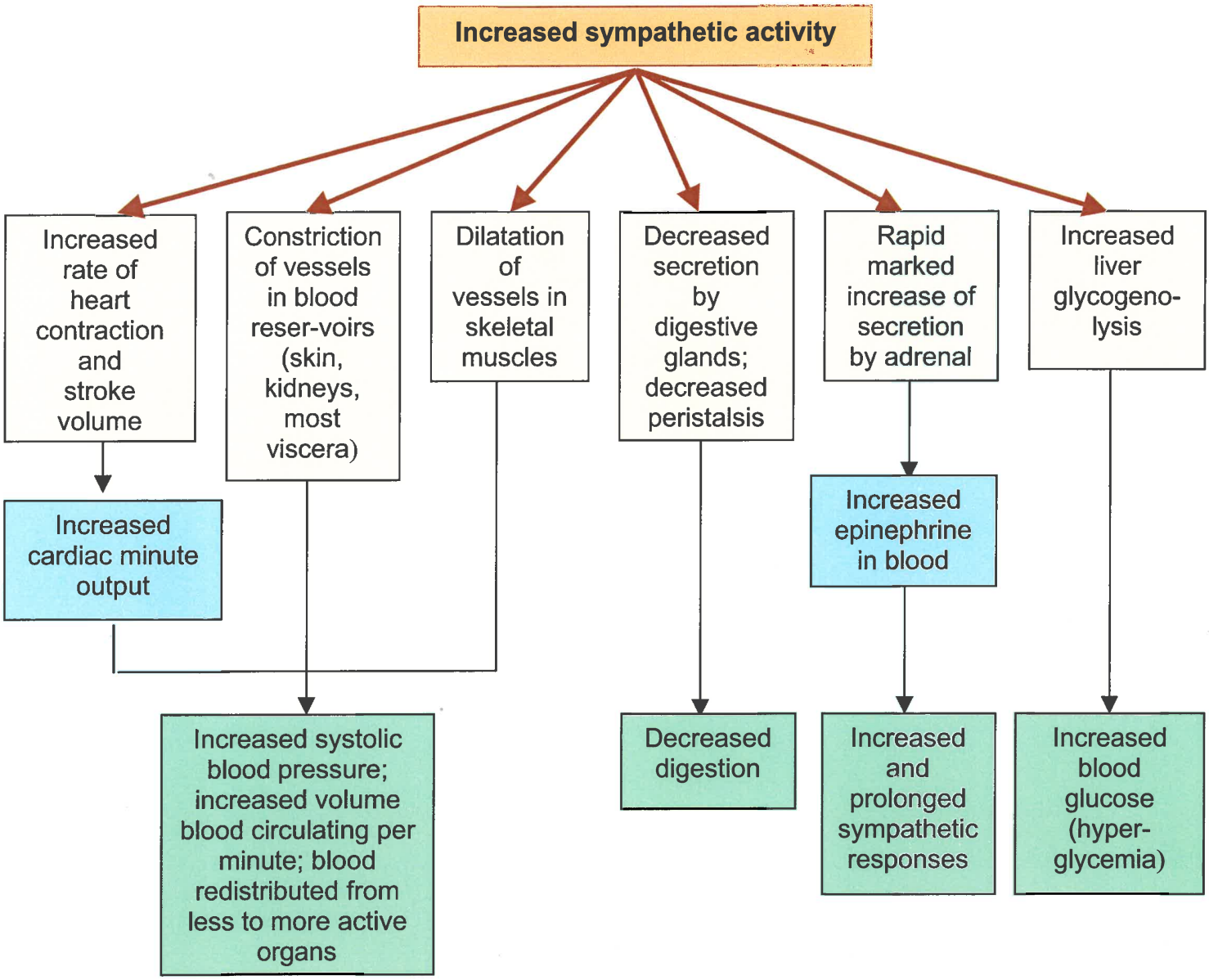

Figure 3.2 : Peripheral effects of general activation of the SAM-axis.

As in the case of the peripheral adrenergic effects, the effects of the central noradrenergic (CNA) system also depend on the postsynaptic receptor involved. These central noradrenergic receptor effects can be summarised by saying that postsynaptic beta-adrenoceptor and presynaptic alpha-2-adrenoceptor effects are generally of an inhibitory nature, while excitatory effects are commonly associated with alpha-1-adrenoceptor stimulation. As such beta-stimulation has been implicated on the ability to concentrate on the task at hand, while inhibiting the influence of irrelevant information, and alpha-1 activation with arousal, the transition from sleep to wakefulness, and the augmentation of registering sensory information about the environment. Impairment of the latter is said to have a bearing on the symptoms of dissociation, which is a characteristic of several behavioural states (4).

Published findings in support of the existence of an association between the central noradrenergic (CNA) system and specific behavioural functions in animals include

- defensive and/or aggressive behaviour upon noradrenergic infusion into subcortical areas (10)
- increases in the firing rates of locus coeruleus neurons upon real or perceived threats (11,12)
- significant increases in locus coeruleus activity, defensive behaviour as well as blood pressure and heart rate, upon exposure to potentially dangerous elements (13)
- fear and anxiety-related behaviour upon stress-induced increases in locus coeruleus activity (14)
- fear and anxiety-related behaviour upon pharmacologically-induced increases in the firing of locus coeruleus neurons, or increases in noradrenaline secretion (11,15,16)
- suppression of locus coeruleus firing rate and noradrenaline release during rest, sleep, white noise, feeding and grooming (17,18,19,20)
- the noradrenergic modulation of amygdalar functions and by implication of the influence of emotion on memory formation (21)
- the promotion of waking and the inhibition of REM-sleep (22) by noradrenaline

- higher levels of the enzymes involved in noradrenaline production in rats bred to attack (23)
- a role for noradrenaline in both the initiation and termination of food intake (24)
- the role for noradrenaline in pathways involved in pleasurable or reward sensation (23)

It has been shown that chronic stress can facilitate locus coeruleus activity through presensitisation - probably through suppression of the central alpha-2-adrenoceptor inhibitory function (4). It is suggested that the results of this presensitisation of animals, as a result of earlier stressful life events, might be extrapolated to human panic disorders, the post-traumatic stress syndrome (PTSD) and the acute combat stress reaction (ACSR) (25). The concept of presensitisation by the central stress response concurs with the finding that childhood abuse in humans would appear to presensitise the individual to the development of combat-related post-traumatic stress disorders in adulthood (26).

It is undeniable that perception does influence the outcome of the psychoneurological interaction. Conceptualisation of the word perception is, however, somewhat problematic when applied to animals. Anxiety is said to be an example of an animal behavioural function that can be seen as a perception-related phenomenon. This in view of the fact that the anxiety response in animals has in the past been described as a maladaptive fear response, i.e., a fear response in the absence of an appropriate virtual threat (27). Examples of the association between anxiety and increased activity of the CNA/SAM-axis were referred to earlier.

The role of perception in the interaction between the behavioural functions and the CNA system is further evident from the results of experiments on conditioned fear in animals. Central noradrenergic activity is said to be involved in this type of reaction where the fear response is provoked by means of a conditioned stimulus (28,29). A great deal of factual information on the interaction between the behavioural functions and the CNA/SAM-axis has, in fact, been derived from this type of experiment and some of the insight obtained from such animal studies contributed to our understanding of the underlying neurological

mechanisms of a number of psychological disturbances in man. Noteworthy results, from animal conditioning experiments, showed the following

a. Increased locus coeruleus activity during fear conditioning, but not during reward conditioning (11)

b. Overactivity-induced noradrenaline depletion of CNA contents to strengthen the response to contextual cues, but to inhibit the fear response to explicit cues (30)

c. The amygdala to be involved in the role of the CNA/SAM-axis in the development of conditioned responses, and perhaps more specifically, fear and anxiety related responses (4), in that

- the amygdala discriminates between noxious or rewarding as opposed to neutral experiences, and as such rules between stimulation and non-stimulation of the CNA activity
- the amygdala is instrumental in the peripheral expression of the conditioned fear response where noradrenaline appears to act through the central nucleus of the amygdala
- the amygdala is involved in the extinction, or stress-induced CNA-modulated non-extinction, of the conditioned response (the extinction of a conditioned response, upon exposure to the conditioned stimulus alone, entails the suppression of subcortical areas such as the amygdala, by cortical areas)
- noradrenaline release in the amygdala is said to help integrate the sensory aspects of experiences pertaining to conditioning as such influences modulate the conditioned emotional response
- amygdalar lesioning prevents the acquisition of conditioning, both in response to specific cues and to context

d. Pathways between the CNA system and the hippocampus to be involved in the neurological processes of conditioned responses (4, 9),in that

- hippocampal lesioning does not abolish the acquisition of fear-related responses to cues, but does interfere with the acquisition of conditioned emotional responses to context (noradrenaline is involved in the role of the hippocampus in conditioning related to spatial context)

- noradrenaline release in the hippocampus may help to integrate the various aspects of a new experience which contributes to the recall of the original aversive events
- the hippocampus, under the influence of the CNA system, may contribute to the stress-induced extinction failure of conditioned fear responses

e. A role for the CNA system in the modulation of the acquisition and retention of memory, in the attentional component of memory storage, in the age-related deficits in working memory and in memory retrieval or recall such as in trauma-related flashbacks (4, 9).

The information described above is derived from experiments in animals where the perception of adverse circumstances, induced through the process of conditioning, lead to alteration of central noradrenergic activity. It is easy to imagine how some of the psychoneurological interactions described may relate to psychological dyshomeostatic phenomena, including traumatic recall of combat-related post-traumatic disorders, the failure to eliminate conditioned emotional responses in patients with phobic anxieties by repeated exposure to the phobia inducing stimuli, as well as the cognitive impairment associated with panic disorders.

The link between the CNA/SAM-axis system and the behavioural functions, as for interactions between other physiological systems and the behavioural functions, are often best observed in situations perceived as extreme by either the body or the mind. It is clear from previous paragraphs that the extreme conditions referred to in the previous sentence are, where animal experimentation is concerned predominantly of an aversive rather than a pleasurable nature. The physiological changes which occur as a result of adverse psychological conditions or perceptions - especially those experienced chronically and perceived as uncontrollable - are seen as maladaptive, and often as incompatible with normal functional integrity. Such changes are peripherally expressed in symptoms like the stress-induced triad consisting of intestinal ulcers, atrophy of lymphoid tissue and hypertrophy of the adrenal glands, as well as cardiovascular, immunological and other abnormalities (the immunological stress-induced alteration of the two main stress axes

are discussed in Chapters 4 and 5). Central nervous system symptoms and even death may also occur. This in contrast to the positive, pro-adaptive neurological effects ascribed to acute activation by mild, intermittent, controllable stressors or by states of eustress. Despite the negative association between chronic, uncontrollable stressful situations and the adverse effects on physiological, as well as psychological well- being, it appears imperative that the neurological system be able to undergo favourable stress-induced anatomical, biochemical and/or physiological adaptations in order to meet novel psychosocial and environmental demands. Anatomical, biochemical and functional alterations have indeed been shown to occur in the brain of animals under certain conditions. Some such changes are seen in Table 3.1. In compliance with the context of this chapter, the changes listed in the table are limited to those pertaining to the central noradrenergic system.

Table 3.1: Modulation and modification of the central noradrenergic system by environmental and psychosocial influences (stress adaptation and presensitisation)

1.	Stress induced increases in synthesis, content, turnover, and release of noradrenaline. Increased production of NA results from ↑ tyrosine hydroxylase (TH) mRNA. The *c-fos* is stimulated by CRF and NA	31,32, 33,35,36, 37,38
2.	Firing rates of NA neurons of the locus coeruleus are increased by controllable stressors	39
3.	Multiple exposures to the same moderate controllable stressor lead to presynaptic axonal sprouting and an increase in cortical noradrenergic innervation which in turn lead to a decrease in receptor reactivity as a result of decreased β-adrenoceptor density (receptor down regulation)	40,41,42, 43
4.	Prolonged exposure to severe uncontrollable stress leads to a decline in cerebral NA concentration, NA release and tyrosine hydroxylase activity (stress presensitisation)	32,44,45, 46

5.	Prolonged severe stress causes retraction of degeneration of cerebral noradrenergic fibres (stress-induced cerebral damage)	40
6.	Intermediate stress with different stressors leads to an increase in central noradrenaline turnover but no presynaptic adaptations. This is dependent on previous stress-induced facilitation	31,32,33, 47
7.	Suppression of NA release, loss of noradrenergic innervation and decreased noradrenaline content in the frontal cortex are associated with uncontrollable stress-induced behavioural abnormalities	48,49,32, 50,51
8.	Chronic stress leads to degeneration of NA neurons in the rat cerebral cortex	52
9.	Chronic restraint stress decreases noradrenaline transporter binding sites in the amygdala, hypothalamus and locus coeruleus	53
10.	Stress exposure is associated with augmentation of the firing rate in the locus coeruleus with concomitant increase in the release and turnover of NA in relevant cerebral areas that receive noradrenergic projections	4,9
11.	Stress-induced noradrenaline secretion modulates gene transcription	4

Examples of the modulation and modification of the CNA system, shown in Table 3.1 provide corroboration that psychosocial and environmental influences are indeed instrumental in alterations of the neurological, and in this case CNA, system. Negative effects of stressors on the CNA/SAM-axis would appear to be fairly well documented. A negative influence, particularly well illustrated, is the previously described presensitisation of the neonatal noradrenergic system as a result of early exposure to unfavourable psychosocial influences. The fact that this type of neonatal presensitisation

of the noradrenergic system can predispose to the development of fear and anxiety related psychological disorders in adult life is supported by the results from both animal and human studies. Despite the general impression of the negativity of stressor endurance, it is well known that behavioural adaptation to stressors may eventually occur and that such experiences would often lead to the enhancement of appropriate coping skills. It is thus conceivable that relatively permanent neurological changes would constitute part of an adaptational process to moderate experiences or stressors. As such it would then form part of the development of coping strategies in response to a specific external or internal condition. Such central, and perhaps peripheral, nervous system alterations may potentially be major converting factors, whereby psychological stressors, erstwhile considered moderately uncontrollable, could be rendered perceptionally controllable. The plausibility of such an adaptational role for stress in the CNA/SAM-axis-psychological interaction would be argued further at a later stage.

In conclusion it can be said that animal experiments provide ample physical evidence for the interaction between the noradrenergic system and the behavioural functions. Such evidence, in view of the invasive nature of the experimental procedures, is unlikely to be derived from human experimentation or human observations. One major disadvantage of applicable animal research, however, is the inability to investigate the neurological-behavioural interaction in terms of a finer discrimination between the various psychological phenomena. The following number of paragraphs will attempt to deal with such aspects in man.

3.2 Psychoneurological Interaction in Man

In the previous section undeniable physical evidence was presented for the psychoneurological interaction in terms of the CNA/SAM-axis system. The aim of the present writing is to endorse the existence of the proposed interaction by documenting some of the associations reported to exist in humans between the behavioural functions and the CNA/SAM-axis.

Although the pathways and mechanisms of action were largely unknown, the central noradrenergic system has long been associated with behavioural functions such as arousal, vigilance, concentration, memory, fear, anxiety, aggression, hostility, agitation, resentment, pleasure, alertness, vigilance, arousal, as well as with enhanced activity of the peripheral sympathetic nervous system. (55,56,57). Evidence for some of these associations in animals were provided in the previous section that dealt with animal experimentation.

Identifying the physiological mechanisms underlying the different behavioural functions has always been problematic. During recent times at least some of the mysteries concerning this mind-body link, i.e., the pathways and mechanisms that have a bearing on psychological processes, were solved. The research involved in exploring the psychoneurological interaction is, however, still confounded by many factors - not least of it the interdisciplinary nature of the field. In animals the physical confirmation of the psychoneurological interactions are generally obtained by means of rather invasive experimental procedures. In man a major part of the relevant research has to rely on indirect assessments as major invasive experimental procedures are not possible in humans. These confounding factors are also applicable when examining the mind-body link in terms of the CNA/SAM-axis. Alterations in central noradrenergic functions are assessed, predominantly, by indirect measures such as a) changes in peripheral adrenergic activity, as reflected by factors such as heart rate and blood pressure, b) plasma catecholamine and catecholamine metabolite levels, c) urinary catecholamine and catecholamine metabolite levels, as well as 24hr excretion of the 3-methoxy-4-hydroxyphenyl-glycol (MHPG) metabolite, d) adrenergic receptor expression on circulating blood cells, e) post-mortem CNS receptor determinations, f) pharmacological modulation of the noradrenergic system by agonists and antagonists, and g) noradrenaline spill-over rates. As for all indirect assessments, each of these techniques poses certain potential errors in the estimation of central noradrenergic activity. With the development of newer neurological procedures, more innovative techniques are becoming available. A discussion of the merits and disadvantages of such techniques is, perhaps, beyond the scope of this writing. However, one fact that should always be kept in mind is that

chronically high levels of catecholamines may not reflect the stimulation state as receptor down regulation may occur.

Clinical research is often a continuance or in pursuit of indications derived from animal experiments. Although the picture is still far from complete, noradrenergic neural mechanisms and pathways involved in the expression of the behavioural functions are rapidly being identified. A great deal of insight into the noradrenergic effects on the psychological make-up of man is deduced from the connections between the CNA-system and other parts of the brain whose roles are known. It is, for instance, now known that the locus coeruleus-noradrenergic system stimulates the mesocortical and mesolimbic dopaminergic systems that in turn innervate the prefrontal cortex and nucleus accumbens, respectively (58,59,60,61,62,63). As such noradrenaline is involved in anticipatory and other cognitive functions, as well as with functions related to motivation, reinforcement and reward. It is of interest to note that the central noradrenergic system is also involved in the regulation of the prefrontal cortex in a more direct way. This implicates a far-reaching role for the noradrenergic system in the control of the behavioural functions as the prefrontal cortex is known to be involved with most of the higher cognitive functions such as the elaboration of thought. Dysregulation or impairment of the functional integrity of the prefrontal cortex has in the past been associated with behavioural problems such as augmentation of working memory and attention regulation, behavioural inhibition, schizophrenia-like symptoms and attention-deficit/hyperactivity disorder symptomatology (64). Some of these abnormalities are also connected to CNA/SAM-system dysfunction. Pharmacological intervention studies, by means of agonists and antagonists, indicate a favourable effect for noradrenaline on the prefrontal cortex when acting on presynaptic alpha-2-adrenoreceptors, and a detrimental effect when acting on alpha-1-adrenoceptors. It is further suggested that the prefrontal cortex needs the noradrenergic input for optimal functional integrity, but that excessively high levels of adrenergic activity, as with severe emotional stress, may suppress its activity and allow subcortical structures to take over the regulation of the required behavioural responses at a faster rate (64). One could perhaps hypothesise that this biphasic effect might be related to the well-known enhancement of cognitive abilities

seen with moderate increases in central noradrenergic activity as opposed to attention fixation with excessively high noradrenergic activity.

Two other important connections between the locus coeruleus-noradrenergic system and other cerebral areas are that with the amygdala and with the hippocampus. The link with the amygdala is important for information retrieval and emotional analysis pertaining to a stimulus (65,66,67). A very intricate neuroanatomical interaction exists between the hippocampus and the central noradrenergic system. This is further complicated by the fact that central noradrenaline can exert its effects on the hippocampus through presynaptic alpha-2-autoreceptors, through postsynaptic alpha-1-adrenoceptors, as well as through beta-adrenoceptors, and is therefore able to inhibit, to stimulate or to facilitate hippocampal neuronal activity (68). Bidirectional influences between the central noradrenergic and central serotonergic neurons have been identified and both neural systems are involved in similar hippocampus-related cognitive and affective functions (68). Their effects, as seen later, may however, often be of an opposing nature.

A connection of major importance with regard to the interaction between the behavioural and the physiological functions is that between the central noradrenergic system and the paraventricular nucleus. The connection comprises a positive, reverberatory feedback loop of activation between the central corticotrophin-releasing neurons and the locus coeruleus noradrenergic neurons and thus between the CNA/SAM-axis and the corticopin releasing hormone/ hypothalamo-pituitary-adrenal axis (CRH/HPA) (55). It is often, through this positive feedback association, that many of the behavioural phenomena find expression. This multi-faceted interaction is, however, a further confounding factor in identifying the primary neurological impairment of related behavioural dysregulations. More about that later in this chapter.

Undeniable evidence exists for the role of the noradrenergic system in learning (69). However, it is as yet not possible to define its exact role in learning behaviour. This despite a vast amount of work on the role of the CNA/SAM-axis in processing and integration of sensory and motor information. In view of the multiple influences of the

noradrenergic system on the rest of the central nervous system, including those on the amygdala, hippocampus and cortex, it is obvious that the CNA system must have at least strong indirect effects on learning behaviour. The connections between the CNA system, the amygdala and the hippocampus were referred to earlier in this chapter. The amygdala and hippocampus are known to be important for implicit, as well as explicit emotional memory, respectively. Strong evidence for noradrenergic involvement in learning and information retention in humans comes from pharmacological experiments and clinical studies where drugs with pro-catecholaminergic actions were shown to enhance learning and retention, and drugs with the opposite effect, seemed to impair such processes (69). An interesting observation is that destruction of the locus coeruleus does not seem to have a major impact on the learning process (23). The involvement of the CNA system in neonatal learning has also been shown in a study where the system would appear to be essential for recognition through preferred tactile and odour identification (70).

Another interesting observation is the fact that peripheral adrenaline, secreted from the adrenal medulla in conditions of stress, is said to have a positive influence on memory, and by implication, on the learning process (71). A pathway by which peripherally secreted adrenaline in response to stress may exert its central nervous system influence is suggested in Figure 3.3. In this pathway circulating adrenaline is said to have an effect on the vagus nerve, which would influence the nucleus tractus solitarius (NTS), which then, in turn, would stimulate the noradrenergic neurons of the locus coeruleus, which have widespread connections with the amydala and hippocampus - two structures intimately associated with learning and memory.

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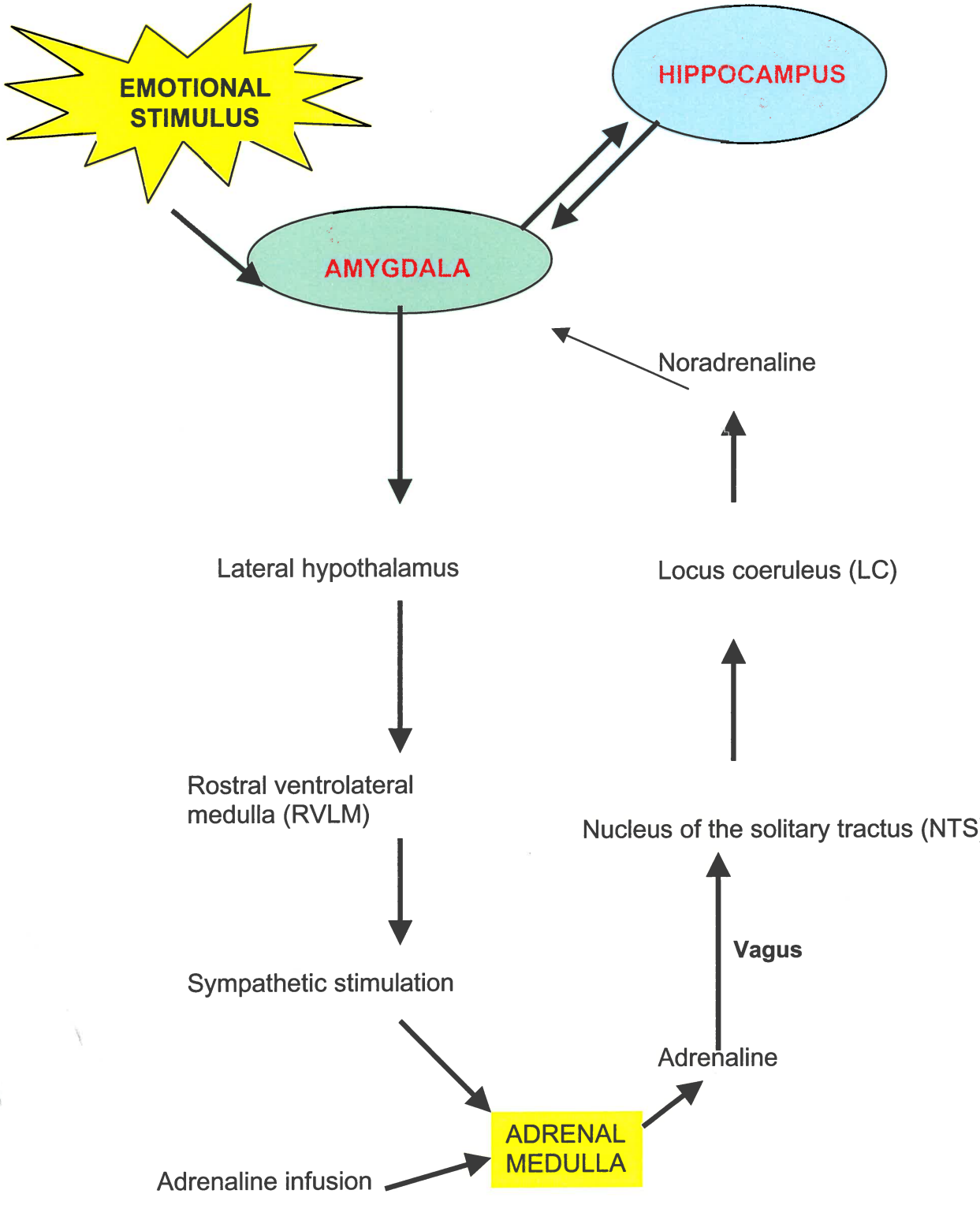


Figure 3.3: The influence of stress-induced peripheral adrenaline secretion on learning [Figure 3.3 shows how an emotional stimulus will activate the sympathetic nervous system, that in turn will increase adrenaline release. Adrenaline, through its effect on the vagus nerve, would lead to activation of the noradrenergic system of the locus coeruleus, which would facilitate the learning processes by the amygdala and hippocampus.] Adapted from (71).

In humans, in contrast to animals, it is possible to define the psychoneurological interactions in terms of more specific aspects of the behavioural functions. Unfortunately, research on this psychoneurological interaction in man, as for animal research, is focused largely on the interaction under adverse conditions, or in individuals with some or other psychological imbalance. Learning and sometimes personality, constitute two of the few behavioural phenomena studied in relation to the CNA/SAM-axis system that do not pertain to adverse environmental or psychosocial conditions, or do not involve a dysregulation of some or other psychological function.

It is fairly predictable that researchers should have tried to find a correlation between personality and the noradrenergic system. This is especially true where the Type A behavioural pattern is concerned, which, according to Friedman and Rosenman (72), conforms to the following:

- reliable components : loud voice, quick speech, enhanced psychomotor activity, tension of facial muscles
- attitudes and emotions : hostility, impatience, anger, aggressiveness
- motivational aspects : achievement motivation, competitiveness, leaning towards success and ambition
- evident or open behaviour: hyperactivity, alertness, celerity, work involvement
- cognitive aspects: control and attributional style

The above behavioural characteristics of the Type A person, in combination with the association of high blood pressure in this type of personality, would in itself be suggestive of high central and peripheral noradrenergic activity. This association is supported by a significant number of publications. There are, indeed, strong indications to suspect Type A personalities to have fast-activation-slow-recovery type psychological profiles (73). Of interest is the fact that this type of personality would appear to display the noradrenergic hyperactivity, as evidenced by cardiovascular and neurohormonal traits, during stress, as well as under basal conditions (74). It is possible that this may

contribute to the epidemiological findings of increased coronary risk. As mentioned earlier, examples of behavioural states associated with augmented noradrenergic activity include augmented vigilance, concentration ability, anger, aggression, irritability, restlessness, fear, anxiety, anticipation, certain perceptions and many others. The involvement of the adrenergic system in such behavioural states is confirmed by intravenous infusion of catecholamines and by symptoms seen in patients with tumours of the adrenal medulla. An increase in the activity of the CNA system, with concomitant hyperactivity in the peripheral sympathetic system (SAM-axis), has indeed been shown to occur in normal, healthy individuals in any situation where substantial emotional activation is present. Aggression is one of the emotions most often associated with noradrenergic function. Most of the evidence for a CNA/SAM-axis role in aggression is derived from peripheral catecholamine shifts. A change in the circulating noradrenaline: adrenaline (NA:A) ratio is a characteristic often seen in aggression, but may be found in many other states of emotion. One could with a fair amount of certainty say that a reduced NA:A ratio would probably refer to a greater HPA-axis involvement in an emotion as the stimulatory effect of the axis on adrenomedullary enzymes is a well-established fact. It is said that the "fight" sympathetic response, or active aggressive emotional display, is primarily associated with an increase in the NA:A ratio, and the "flight" or tense/passive/apprehensive emotional display of the fight-or-flight reaction, with a decrease in the NA:A ratio. The above assumption is supported by the findings of higher urinary noradrenaline levels in persons who are chronically irritable, resentful and angry, while a more significant increase in urinary adrenaline is said to be seen with generalised fearfulness and doubt (75). This may, again point toward an HPA-axis involvement as mentioned in the chapter dealing with the psychoimmunological interaction. Further support for a role of the noradrenergic system in aggression is derived from the aggression seen in normal animals treated with some drugs used to augment noradrenergic activity in depressive humans (76). Extrapolations to therapeutic implications are self-evident.

Temperament-related behaviours such as inhibition or aggression are known to be related to early childhood biological responses to social adversities. Based on results from a

sizeable number of investigators it is suggested (77) that autonomic reactivity in the so-called *easy child* is likely to be characterized by a high stimulus threshold and a quick return to baseline values (strong dampening). The difficult child, in contrast, is said to have a low autonomic threshold, slow return to baseline levels and a high predisposition for re-activation upon repeated stimulation (77). The individual contributions of the CNA/SAM-axis and the cholinergic system, respectively, to the altered autonomic balance are not clear. It is also not clear whether this psychobiological contrast between the easy and difficult child is to be ascribed to genetic differences or to early psychosocial preconditioning. The answer is probably to both. Similar presensitisation of the noradrenergic system to the combat-related stress syndrome has been described earlier in this chapter.

Most of the behavioural symptoms described in the last couple of paragraphs occurred in normal healthy individuals in reaction to the context of the situation, where the associated enhanced noradrenergic activity occurred as an acute change from baseline levels. It is, however, clear that the CNA/SAM-axis may very well be involved in a number of behavioural disturbances. The best substantiated indications for an association between noradrenaline and behavioural disorders are those pertaining to the fear and anxiety related disorders. Evidence supporting, as well as evidence refuting such a virtual relationship can be seen in Table 3.2, as adapted from recent reviews (4,9). References to the original authors can be found in the articles (4,9).

Table 3.2: Evidence for and against the involvement of the CNA/SAM-axis in fear and anxiety-related disorders (4, 9).

Disorder	**Supportive *vs* non-supportive publications**
1. Panic disorder	
Increased resting heart rate	5 vs 4
Increased resting blood pressure	1 vs 3
Increased resting heart rate in panic-prone patients	1 vs 1

Increased heart rate response to orthostatic challenge	1 vs 0
Increased heart rate during panic attacks	6 vs 2
Increased blood pressure during panic attacks	2 vs 2
Increased plasma noradrenaline	1 vs 5
Increased plasma adrenaline	2 vs 0
Increased resting urinary adrenaline and noradrenaline	2 vs 1
Increased plasma MHPG at baseline	0 vs 3
Increased plasma MHPG during panic attacks	1 vs 2
Decrease in lymphocyte β-adrenergic binding sites	1 vs 0
Decrease in basal activity of cAMP	1 vs 0
Decreased platelet alpha$_1$ binding sites (B_{max}) for clonidine	1 vs 1
Decreased platelet alpha$_2$ binding sites (B_{max}) for yohimbine	3 vs 2
Decreased platelet alpha$_2$ receptor affinity (K_D) for clonidine	0 vs 1
Decreased platelet alpha$_2$ receptor affinity (K_D) for yohimbine	1 vs 0
Decreased platelet alpha$_2$ (B_{max}) and (K_D) for [^{3}H] rauwolscine	0 vs 1
Reduction in panic anxiety with clonidine	4 vs 1
Blunted growth hormone response to clonidine	4 vs o
Increased plasma MHPG with yohimbine	5 vs 0

2. Posttraumatic stress disorder

Increased resting heart rate	5 vs 5
Increased heart rate and blood pressure response to traumatic slides and sounds	5 vs 0
Increased heart rate and blood pressure response to traumatic scripts	4 vs 0

Increased resting urinary noradrenaline	2 vs 2
Increased resting plasma noradrenaline	0 vs 1
Increased plasma noradrenaline in response to traumatic reminders	1 vs 0
Increased plasma adrenaline in response to traumatic reminders	1 vs 0
Increased startle reaction	1 vs 1
Decreased binding to platelet alpha$_2$ receptors	1 vs 0
Decrease in activity of cAMP	1vs 0
Decrease in platelet monoamine oxidase activity	1vs 0
Increase in PTSD and plasma MHPG with yohimbine	1vs 0
Differential effect of yohimbine on brain metabolism	1vs 0

3. Generalised anxiety disorder

Increased plasma noradrenaline	3 vs 1
Increased plasma adrenaline	2 vs 0
Increased plasma MHPG	2 vs 0
Increased monoamine oxidase activity	1 vs 0
Decreased platelet alpha$_2$ adrenergic binding sites	1 vs 1
Blunted growth hormone response to clonidine	1 vs 0
Behavioural and biological responses to yohimbine	0 vs 1

4. Phobic disorders

Increases in heart rate, blood pressure, plasma, noradrenaline and adrenaline with phobic stimulus in simple phobia	1 vs 0
Increased plasma noradrenaline in social phobia	1 vs 0
Blunted growth hormone reponse to clonidine in social phobia	1 vs 0

5.	**Obsessive-compulsive disorders**	
	Increased plasma noradrenaline	1 vs 0
	Increased plasma MHPG	1 vs 1
	Blunted growth hormone response to clonidine	1 vs 3

MHPG = 3-methoxy-4-hydroxyphenylglycol

The results from the studies referred to in table 3.2 almost uniformly support the assumption of increased noradrenergic activity during the attacks of patients suffering from panic disorders. Controversies still exist with regard to baseline activity, with some workers reporting raised levels, and others contradicting it. An increase in cerebral responsiveness is suggested, possibly involving alpha-2 receptor dysregulation. Similar results were found in the posttraumatic stress syndrome - again implicating alpha-2-receptor functional alterations. Indications from studies in patients with the generalised anxiety disorder also implicate the noradrenergic system, but it is unlikely that dysregulation of the central alpha-2-adrenoceptor be a major factor in the behavioural dysfunctioning. Although baseline catecholamine and catecholamine metabolite (MHPG) levels were seen to be augmented in phobic and obsessive-compulsive disorders, no conclusive results could be obtained by means of receptor agonist or antagonist studies. It is thus unlikely that the central noradrenergic system should represent the primary neurological impairment in either phobic or obsessive-compulsive disorders. The reason that the CNA/SAM-axis would appear to be strongly implicated as a primary contributor in panic and posttraumatic disorders, in contrast to that in the others, is suggested to be related to their direct pertainment to the stress response (9).

Examples of other associations between the CNA/SAM-axis and some defined behavioural functions and disorders in humans can be seen in Table 3.3.

Table 3.3: Examples of behavioural characteristics and psychiatric disorders associated with variations in noradrenergic activity.

Characteristic/disorders	Reference
Stress Link between central noradrenergic sympatho-adrenomedullary outflow and stress is an established fact (see text for further discussion)	78, 4, 9
Cognition Noradrenaline influences cognitive function through both alpha-1 and alpha-2 adrenoceptors	79
Sensation-seeking Possible association between noradrenergic dysregulation and sensation-seeking in youths with behavioural problems	80
Reward dependence Hypophysis that reward-dependent traits are partially determined by central noradrenaline	81
Pathological gambling A role is suggested for the central noradrenergic system as mediator of the selective attention trait of pathological gambling	82
Substance abuse Possible link between dopaminergic/noradrenergic dysfunction and substance abuse as well as antisocial behaviour	83
Alcohol dependence Changes in the levels of neurotransmitters such as NA	84

Conduct disorder	
Possible decreased NA-functioning (↓ production)	86 (p1072)
Attention-deficit hyperactivity disorder	
↓ adrenaline and ↓ noradrenaline in attention-deficit hyperactivity disorder	86 (p1064)
A multistage hypothesis as an update on the catecholamine hypothesis	93
Tourette's disorder	
Above normal NA-activity implicated by the effects of alpha-adrenergic agonists. May, however, merely reflect an indirect effect on dopaminergic activity	80
Paraphilias in males	
Monoamine hypothesis for paraphilias	94
Fear and anxiety-related disorders	
Extensive evidence for noradrenergic hyperactivity and alpha-2-adrenoceptor dysfunction.	See Table 3.2
Increased firing of locus coeruleus neurons associated with behavioural manifestations of fear	4, 9
Anxiety disorders	
Strong association between high NA-activity and anxiety.	86 (p576,612)
Dysregulation of the central NA-system with periodic activity bursts (General theory)	
Possible subsensitivity of alpha-2 receptors in anxiety disorders	
Proposed anatomical basis of anxiety and network of related brain regions involved in the genesis of anxious behaviour	95
Maladaptive reponses to stress in both the HPA-axis and SAM-axis (Review)	96

Post-traumatic stress disorder (PTSD)

Hyperactivity of at least the noradrenergic system	86 (p607)
Two different subgroups of PTSD; one with a sensitized NA-system, the other with a sensitised serotonergic system	97

Panic disorders

Increased sympathetic tone and central NA-activity implicated as contributing factors	86 (p583)
A functional neuro-anatomical/neurochemical model	98
Increased NA-reponsiveness in panic disorder without changes in baseline NA-function	9 and 4

Phobias

Adrenergic theory for social phobias - augmented secretion of central and peripheral NA and A and hypersensitivity to NA-stimulation	86 (p594)

Depression

Interaction between NA and serotonin a confounding factor in defining the exact role in mood disorders. The biogenic amine hypothesis: Mood disorders associated with heterogeneous dysregulation of biogenic amines such as NA. Decrease in central NA-activity, perhaps as a result of excessive alpha-2 receptor activation. NA activity varies depending on type, severity and phase.	86 (p139)
Higher sympatho-adrenal activity in major but not in minor depression. NA-activity related to HPA-axis activity.	99
The adrenergic-cholinergic imbalance hypothesis.	100
Serotonin-noradrenaline link hypothesis of affective disorders: a receptor-receptor interaction	101
Sympathetic nervous system activity is augmented in major depression	102

(Prolonged administration of desipramine leads to alpha-2 desensitisation and tricyclic antidepressants to reduced NA clearance)	
Depressed patients, especially melancholic and unipolar, excrete above normal amounts of NA and demonstrate subnormal biochemical and neuroendocrine responses to alpha-2 adrenergic agonists	103
Stronger link suggested between depressed states and adrenomedullary activation than depression and sympathetic system. This for unipolar as well as bipolar states	104
Hypothesis that stress-induced activity in the HPA-axis may be the cause of the abnormal noradrenergic activity of depression	105
Decrease in the NA transporter (NET) in the locus coeruleus neurons implicated in major depression	106
Results with non-psychotic major depressive disorder subjects indicate the HPA abnormality to be related to alpha-2 adrenoceptor dysfunction	107
Clinical improvement of melancholic/psychotic depressive illness after ECT-induced lowering of plasma noradrenaline	108
Abnormalities of alpha-2 and beta adrenoceptors in depression	109

Schizophrenia

Evidence from literature points towards an increase in the central noradrenergic activity and perhaps an alpha-2 receptor dysregulation, depending on severity and stage of affliction. In summary a) it is questionable whether NA alterations are primary to schizophrenia, b) abnormal NA-,metabolism of NA-response to stress may however be implicated in some patients and c) NA is without doubt involved in the modulation of dopamine (see dopamine hypothesis of schizophrenia)	86 (p464)
Hypothesis of multiple neurotransmitters involving complex circuitries. (Implicating a role for the NA-system)	110

Alzheimer's disease

Decrease in noradrenergic activity and decreased number of noradrenergic neurons in locus coeruleus	80 (p346)
Loss of NA neurons contributes to the development of the non-cognitive behavioural impairments of Alzheimer's disease	111

NA = Noradrenaline; 5-HT = 5-hydroxytryptamine (serotonin)

It is by now generally accepted that a dysregulation of the noradrenergic system is involved in the pathogenesis of mood disorders. Several references to this effect can be seen in Table 3.3. Patients with depressive disorders, especially melancholic unipolar subjects, are known to have higher levels of circulating noradrenaline levels than normal and to excrete greater amounts of catecholamine metabolites through their kidneys. Subsensitivity of the alpha-2 adrenoceptors is presumed to be involved in the exaggerated noradrenergic response to environmental and psychosocial stimuli. However, noradrenergic dysfunction is unlikely to be the sole, or perhaps even the major, neurological impairment in mood disorders. This statement may very well be debatable as results from studies on the alpha-2 and beta-adrenoceptors seem to indicate a central role for the central noradrenergic (CNA) system in depression. A variety of other neurohormonal disturbances have, however, also been implicated in depression. Of special interest, with regard to the mood disorders, are the findings of co-existing dysregulations in the CNA/SAM-axis with that in other neurohormonal systems. Some of them are referred to in Table 3.3, and a few examples of such coupled dysregulations will briefly be discussed in the following paragraphs.

- Concomitant dysregulation in both the CNA/SAM-axis and the CRH/HPA-axis is said to occur in severe depression (99). This is a major confounding factor in the search for the primary causative factor. In view of the reverberating positive feedback loop known to exist between the two axes, the primary disturbance may be either a) a disturbance in a common denominator to both axes, b) high sympatho-adrenal (SAM) tone as a result of sustained stimulation by glucocorticoids and/or opioids, i.e.,

augmented SAM-axis activity secondary to high HPA-axis activity, or c) a primary noradrenergic hyperactivity with a resultant secondary hyperactivity in the CRH/HPA-axis, due to the positive feedback interrelationship between the two systems (99). A simultaneous dysregulation in the two axes could, whatever the primary disturbance, lead to the exacerbation of a number of their respective behavioural effects and may, depending on the magnitude and equilibrium shift of the response, have other far reaching psychological effects. This in view of the similarity, and subtle, yet important, differences in their behavioural effects. It is important to note that simultaneous hyperactivation of the noradrenergic and HPA-axes is in no way limited to mood disorders. The stress-induced co-activation of the two systems is well known, but co-activation in other conditions or situations, such as anxiety-related disorders (112), panic- related disorders (96) and the Type A personality pattern (74), has also been reported. It might very well be that the co-activation represents a mere reflection of the activation of the generalised stress response.

- Another co-existing neurohormonal disturbance involving the central noradrenergic system that has been implicated in the mood disorders is that with the central serotonergic system. Approaches to this interrelationship differ, but the neuroanatomical interconnections and functional bidirectional influences between the two systems had already been described more than twenty years ago (113). The original *Serotonin/Noradrenaline Link Hypothesis of Affective Disorders* (114), has, however, been revised, and more recent evidence (115) indicates the serotonin-noradrenaline interaction to be a receptor-receptor interaction which involves alteration in the adrenergic beta-receptor density and second messenger activity. *The Serotonin/Noradrenaline Link Hypothesis of Affective Disorders* implicates the multi-component beta-adrenoceptor system to be an integrative/amplification/adaptation system for behavioural functions such as mood, sleep, arousal and pain perception, as well as for neuroendocrine and autonomic regulation. As such this system is suggested to serve an adaptational function against excessive sensory input. Dysregulation of the system is then hypothesised to predispose to depressive disorders (115).

- The coupled noradrenaline-serotonin dysregulation hypothesis as cause of mood abnormalities has also been implicated in various other approaches (105,114). We shortly refer to the implied role of the noradrenergic-serotonergic system as seen by supporters of the plea for a simpler classification model for psychiatric disorders According to this approach it is reasoned that the majority of common psychiatric disorders, excluding psychotic illnesses, are based on two major symptom dimensions, that is, depression-related symptoms and anxiety-related symptoms (116). This in view of the ideology that a simpler model of psychological illness would facilitate our integrative understanding of the subject. Overlapping of symptoms is said to occur as a result of the presence of social factors associated with each symptom dimension and to the fact that depression and anxiety, two reciprocally related phenomena, both relate to reward and punishment, respectively. Functional alterations in the central noradrenergic and central serotonergic systems are in turn implicated in the aetiology for both the symptom dimensions, i.e., depression and anxiety. A biosocial model for common mental disorders, based on this two-sided biological approach, and with further refinement based on three social factors, i.e., vulnerability, destabilisation and restitution, is suggested (116). Should this biosocial view of behavioural dysfunctioning be correct, the noradrenergic-serotonergic interaction would be a major biological factor in the majority of behavioural disturbances. As in the case of the CNA/SAM-CRH/HPA-axes interrelated dysregulation, the noradrenergic-serotonin coexisting dysregulation has also been implicated in several other psychiatric disorders, including the impulse-control disorders (92), alcohol-related changes in behaviour (85), the generalised anxiety disorder (96) and many more.
- A concomitant cholinergic-adrenergic shift is described in the *adrenergic–cholinergic imbalance hypothesis* of depression where the cholinergic–adrenergic balance is said to be involved in the regulation of drive and mood (100) .The hypothesis is derived from the integration of the knowledge on noradrenergic activity in mood disorders, the observation of depressiogenic and antimanic properties of cholinomimetics, and the acute euphoriant effects of anticholinergic agents. The idea of a co-operative connection or influence between the sympathetic and cholinergic systems with regard

to the behavioural functions is also being considered by others and a concept of synergism of sympathetic and parasympathetic activity has been described (117).

- Various other types of neurohormonal shifts, coexisting with alterations in the CNA/SAM-axis, have been reported for a fairly wide spectrum of behavioural disturbances. Systems or substances in which a disturbance, co-existing with that in the central noradrenergic system, are known to occur, include gamma-aminobutyric acid, endogenous opioid peptides, serotonin, glutamine, thyronergic substances, neurohormonal substances belonging to the hypothalamo-pituitary-adrenomedullary (HPA) axis, as well as a number of other neuropeptides (84,96,110,107).

As bidirectional regulatory influences seem to exist between the CNA/SAM-axis and the majority of neurohormonal systems, it is not surprising to find changes in other neurohormonal factors or systems co-existing with that in the CNA/SAM-axis. It is important to note that the so-called neuropeptides also play an important regulatory role in both the central noradrenergic (CNA) and the peripheral sympatho-adrenomedullary (SAM) systems (118).

Another phenomenon that should perhaps be mentioned is the apparent association between the peripheral part of the CNA/SAM-axis and the behavioural functions, i.e., the proposed influence of sympatho-adrenomedullary (SAM) secretory activity on the psychological make-up. Despite the assumption that catecholamines cannot readily cross the blood-brain barrier, central behavioural effects have been reported in the presence of high circulating adrenaline levels. Published examples of this observation include

- Indications from experimental work show that drugs that affect peripheral, rather than central catecholamine levels will attenuate memory retention. An example of this was referred to earlier in this chapter.
- The reported importance of adrenomedullary activity in the symptoms of both mixed and pure mania (119).
- The increase in the circulating adrenaline:noradrenaline (A:NA) ratio in unipolar depression, which points towards a strong adreno-medullary involvement (99).

- The emotional effects, sometimes mimicking psychogenic anxiety attacks, seen in patients with adrenomedullary tumours (120).
- The psychological effects of catecholamine infusion into the peripheral circulation (71).

Several possible explanations can be volunteered in an attempt to explain the above-mentioned association between the behavioural functions and conditions where the major disturbance appears to be peripheral, rather than central. Due to the influence of the locus coeruleus on sympathetic outflow, as well as the dependence of the adrenal medulla on stimulation by preganglionic sympathetic fibres, it would be absurd to interpret a mere increase in circulating adrenaline (A) and noradrenaline (NA), without A:NA-ratio alterations, as an indication of adrenomedullary involvement in the behavioural functions. An explanation for the changed ratio may possibly be the augmentation of adrenomedullary function secondary to the secretory activity of the adrenal cortex. This in view of the commonly known role of the adrenocortical hormones in changing the A:NA ratio of the circulating catecholamine pool and *vice versa* (121). However, the most feasible explanation would seem to be the alteration of central noradrenergic function through an indirect effect of circulating adrenaline. This could be accomplished by circulating adrenomedullary derived adrenaline, influencing the transmission along vagal afferents to the tractus solitarius, which in turn could activate the locus coeruleus , giving rise to the CNA-induced changes in behaviour. A schematic presentation of this was given earlier in this chapter (Figure 3.3).

The coexistence of disturbances in more than one neurohormonal system just described stresses the fact that any hypothesis trying to describe a behavioural syndrome as a *too-little* or a *too-much of one specific neurotransmitter* is bound to be incomplete. This statement, especially with regard to the CNA/SAM-axis, is substantiated by the multiple anatomical-physiological interactions between the noradrenergic and other neurotransmitter/ neurohormonal systems. It would appear that one could at best arrive at a decision on the type of neurohormonal shift typical for a specific behavioural disturbance or, in some instances, at a decision on the primary disturbance. In view of the

widespread connections of the noradrenergic system, as well as the adrenoceptor alteration repeatedly shown in association with variations in behavioural functions, one cannot summarily rule out the possibility of a disturbance in this system as the primary factor in a number of psychological disturbances. It is, however, unlikely that diagnoses, based on such potential neurohormonally-defined patterns, would be possible without considering the psychosocial environment as well as the perception, self-efficacy and coping characteristics of the individual. But then again it should be remembered that coping and self-efficacy influence and are influenced by CNA structure and function.

3.3 The bidirectional interactions between psychological functions and the CNA/SAM-axis

It is not always easy to distinguish between cause and effect with regard to the psychoneurological interaction. It is likely that the interaction may be of a continuously reverberating nature, rather than a simple bidirectional interaction. For this reason no distinction was made in the previous two divisions of this chapter between the CNA's effect on the mind or the mind's effect on the CNA. It is, however, now indisputable and well documented that the physiological-anatomical integrity of the brain can be a determinant of mind and that the mind can affect the body in a variety of ways. This is especially true in the case of the CNA/SAM-axis where the fight or flight reaction occurs in response to cognitive or emotional arousal as discussed earlier in the chapter. The effects of both acute and chronic stress can further influence the CNA/SAM-axis in ways that could, in turn, influence the psychological disposition and even cause or predispose the individual to psychological disorders by changing the structural characteristics.

The decision between cause or effect is less problematic in some cases – especially in situations where deliberate psychological therapeutic interventions are employed in order to bring about physiological and other somatic effects. Examples of what can perhaps be seen as primarily mind-on-body influences are the results obtained by a number of biofeedback interventions, the practice of certain Eastern philosophies, the effects of suggestions made under surgical anesthesia, the effects of hypnosis and possibly that of

cultural healing and psychotherapy. In general terms volumes can be written about the influence of mind-over-body. Linking the impact of psychological factors to specific neural mechanisms is however a different matter altogether. Examples of some of the above in terms of the CNA/SAM-axis are discussed in a writing by Rossi (122), as summarised in the following paragraph. The reader is referred to his writing for the references to the original publications on which the examples in this paragraph are based.

Examples of the CNA/SAM-axis modulation by the mind, discussed by Rossi (122), include phenomena like hypnosis, unconscious learning during surgical anesthesia, coping, and some of the effects derived from practices based on Eastern philosophies. Rossi sees hypnosis as a prime example of the influence of mind-over-body. Many of the effects of therapeutic hypnosis are said to be secondary to sympathetically induced blood flow alterations. Control of sympathetic system-induced circulatory control by the mind is already known to form the basis of a variety of biofeedback therapies. Effects thus obtained through hypnosis include the curing of headaches, the control of blushing, breast enlargement, amelioration of bruises, induction of sexual arousal and erection, curing of warts and dermatitis, production of inflammatory reactions, amelioration of congenital ichthyosis, as well as the control of the alarm response, hypertension, Raynaud's disease, coagulation and the immune response. The second type of examples of physiological-modulation, i.e., noradrenergic system-modulation by the mind, discussed by Rossi, is unconscious learning during surgical anesthesia. This is reported to influence the outcome of the surgical procedure as well as the postoperative recovery. This in response to suggestions made while under the influence of anesthesia and augmented by peripheral administration of adrenaline. Coping under stress is yet another example described in association with the CNA/SAM-axis. Coping, where stress is seen as a challenge, in contrast to non-coping where stress is seen as a threat, is said to be characterised by activation of predominantly the CNA system, while the central activation of both stress axes is said to occur during non-coping. This noradrenergic dominance during coping may perhaps be extrapolated to motivation as the differentiation of the response to stress into the perception of challenge or threat corresponds to Selye's description of eustress and distress, as well as to Abraham Maslow's deprivation motivation as opposed to stress

motivation. The relationship between CNA/SAM-axis activation and coping just mentioned seems illogical in view of the degree of emotional arousal expected. A perhaps more acceptable relationship between coping and noradrenergic activity was reported by Albert Bandura (123) in patients experiencing some kind of phobia where an inverse relationship is said to exist between the sense of coping (sense of self-efficacy) and the catecholamine levels.

Another mind-over-body effect, which involves the noradrenergic system, is the control of consciousness by means of the practises associated with Eastern philosophies. Many examples exist, some of them generally known and others beyond the common knowledge of the average Westerner. They would not be discussed at this point. Enough to say that a link was shown between such practices and central noradrenergic activity.

The examples of the influence of the mind over the CNA/SAM-axis thus far mentioned, are just some of a number of generally well known phenomena. Perhaps lesser known or accepted is the fact that behaviour or psychological reactivity in response to perceptions can have a more permanent impact on, not only cerebral function but also cerebral structure. Some such examples were previously shown under the results from animal experimentation.

The next couple of paragraphs are intended to show that the higher neurological centers are a) more than the hardware where environmental and psychosocial demands are recognised, b) more than the sites from where appropriate or inappropriate behavioural reponses are initiated, c) and more than the structures which, in the presence of functional or structural abnormalities, can give rise to alteration in psychological functionality. It is meant to show that the neural structures are, in fact, also the target organs of perceptions with regard to novel or stressful environmental and psychosocial situations or influences. As such the psychological make-up and experiences would serve as response modifiers of cerebral structure and function. It is suggested that such modifications may then, if successful, form the basis for psychological adaptation or, in the case of maladaptation, for presensitisation to future behavioural disturbances. The discussion, in accordance

with the intent of this chapter, is confined to facts pertaining to the CNA/SAM-axis and the magnitude and depth thereof limited in conformance to the aim of the chapter, that is, to provide the necessary evidence in support of a bidirectional psychoneurological interaction in terms of the CNA/SAM-axis.

The old argument of *nurture* versus *nature* is well known. Under this misconception of posing the one against the other, it was argued that behaviour is determined either by environmental factors, by genetic factors, or by a combination of the two. This type of reasoning was based on the believe that gene expression is autonomous and that the effects of psychological influences on the neurological system are independent of the genome. The realization that the brain can adapt to environmental and psychosocial influences by changing the variable expression of genes (124), brings about a dramatic change in our perspective with regard to behaviour. By taking the potential effect of hormones and neurological transmitters on the genetic variability into account, it becomes obvious that psychologically-induced changes in the neurohormonal profile of an individual can lead to a type of remodeling of neural structure and function, which in itself would have an influence on behaviour. Such neural alterations may either be transient or permanent. It has indeed become conceivable how environmental conditions, as well as internal conditions such as stress, fear, anxiety, trauma, happiness, contentment, or even just the perception of psychosocial conditions, can lead to a shift in behavioural disposition - ranging from adaptation to the stressor, to presensitisation to a stressor, to neurotransmitter imbalances, to psychological disorders and even to neuronal atrophy. One could surmise that the primary aim of such an adaptational capacity would be situated in the psychological development of the individual.

Modification of the neural structures by internal and external environmental influences is nothing new and forms part of the early developmental, as well as of all postnatal learning processes. It is highly likely that such modifications occur throughout the individual's normal life span. Examples of this were given in Table 3.1, where the destructive nature of uncontrollable stress, as well as the developmentally advantageous effects of controllable stress were presented. The suggested cellular and sub cellular

mechanisms through which the noradrenergic system contributes to this implied neural plasticity is beyond the aim of this writing, but can be found in a recent text (125), that deals, amongst others, with the role of the adrenergic system in central and peripheral plasticity, in genetic diseases, as well as with potential gene therapy. Some interesting findings are discussed where behaviour is used to analyse the role of the various aminergic receptors. Most of the experimental evidence discussed were, however, derived from work on lower invertebrata.

Evidence derived from higher vertebrata and from man is available to support the validity of the results from lower invertebrata. It would appear that not only the neurons, but also the central nervous system astrocytes and other structures are involved in the adaptational modification of the noradrenergic system by the psychological experiences. It is also known that noradrenergic activity in the brain has many effects over and above that of membrane potential alterations. Such activities include the activation of second messenger systems in post-synaptic neurons which in turn leads to metabolic alterations and to changes in the responsiveness to incoming stimuli, effects on oncogene expressions, astrocyte modification, blood-brain barrier permeability alterations and more. The specific influences of noradrenergic activity on cerebral function and structure, as well as the effects of sympathetic activation, are shown in Figure 3.3. Such changes are often characterised by a considerable time lag between stimulation and the actual alterations. As such they are postulated to be involved in, or to act as trigger mechanisms for long term adaptive modifications (126). Examples of such non-transmitter functions and modifications of the CNA in response to stressors include

- the noradrenaline/c-AMP-mediated release of glucose and lactate from astrocyte glycogen stores (127) and the exacerbation of the process by stress (128) with subsequent attenuation by repeated exposure to the same stressor (129).
- synthesis and release of growth factors from astrocytes upon noradrenaline release (130).
- the expression of oncogenes such as *c-fos* in neurons (131).
- the role of the central noradrenergic system in developmental cortical plasticity

(132).

- the role of the central noradrenergic system in morphological plasticity and recovery from cortical lesions (133).
- the structural changes in astrocytes upon stress-induced noradrenergic secretion (135).
- transient acute stress-induced beta-adrenergic-mediated increases in cerebral perfusion and energy consumption (136).
- prolonged (chronic) stress-induced decreases in cerebral blood flow (137).
- the apparently beta-adrenoceptor-mediated regional increases in blood-brain barrier permeability (138,139) in response to stress.

Other examples of the psychosocial influence on the central noradrenergic structure and function are available. Certain emotional influences on the CNA/SAM-axis that are of significance to the dissertation as a whole, are those that are in turn involved in the development of a sense of self-efficacy and coping. Although many neural networks are probably involved, a role for the noradrenergic system is suspected – over and above the reference to that effect on earlier pages. It is, however, virtually impossible to embark on a reasonable discussion on the link between such psychological phenomena and the biological alterations, in terms of either the possibility of psychological adaptation or psychopathological development, without reference to the CRH/HPA system. The discussion on such potential implications will therefore be deferred to Chapter 5, which deals with the psychoneurological interactions in terms of the CRH/HPA-axis.

The previous paragraphs focused on the influence of the psyche on the CNA/SAM-axis. The reversed influence, i.e., the role of the CNA/SAM-axis in the psychological disposition, was discussed throughout the first two sections of this chapter. In concordance with the aim of this chapter, as part of a minor subdivision of the study, an in-depth discussion of any one aspect was avoided. The need for a detailed, meticulously executed review of noradrenergic involvement across the spectrum of behavioural functions and disorders has, however, become patently clear. What is, in fact, suggested is a reversed perspective with the focus on one neurohormonal system across the

psychological spectrum, rather than on all neurohormonal aspects of one psychological disturbance. The results of such a study could have marked implications with regard to the relatedness of various psychological phenomena and perhaps to diagnostic criteria. An example of a possible unexpected relatedness may, for instance, be that between impulse-control and bipolar disorders (92) where related CNA system alterations have been shown.

In an attempt to understand the pervasiveness of the influence of the CNA/SAM-axis on behaviour – and thus to see its importance in the psychoneuroimmunological interaction, its behavioural and specific functions were summarised. This is presented as Figure 3.4.

Figure 3.4, i.e., the functions of the CNA-system and the peripheral SAM-system, is inserted on the next page with the legend to Figure 3.4 following on the subsequent page.

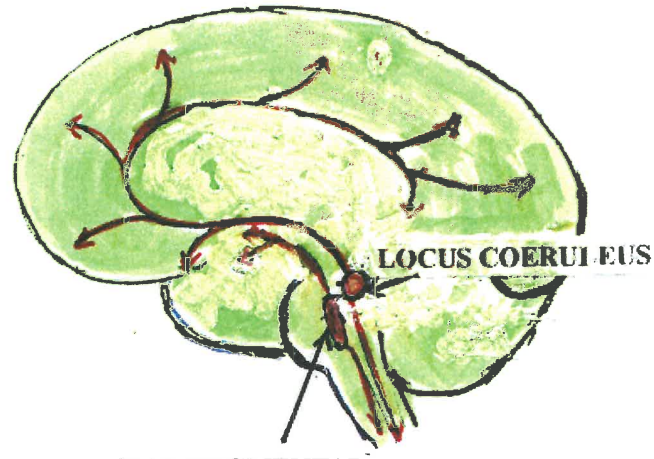
SPECIFIC FUNCTIONS OF THE CNA-SYSTEM.

Behavioural functions
Facilitation of predatory/attack behaviour
Enhanced anxiety-related behaviour
Improved acquisition and learning
Enhanced reactivity to stimulation
Augmented sensory information processing
Accelerated motor responses
Augmented vigilance & facilitation of arousal
Stimulation of the HPA-axis
Propagation and perpetuation of the stress response
Maintenance of non-spatial readiness to external clues
Augmentation of cognitive functions of prefrontal cortex
Regulation of eating behaviour
Involved in cerebral plasticity
Modulates the induction of hippocampal synaptic plasticity

Specific effects on neurons
Changes excitability and information processing
Increases signal-to-noise ratio
Enhances target selection
Role in lactation-induced synaptic plasticity
Modulates central thyronergic activity
Activates central second messenger systems
Alters protein phosphorylation
Alters metabolism & gene expression

Specific effects on astrocytes
Activation of second messenger systems
Alters protein phosphorylation and glycogen metabolism
Alters gene expression

General physiological and anatomical effects
Modulation of forebrain electroencephalographic activity
Increases cerebral blood flow and metabolism
Increases blood-brain barrier permeability
Facilitation of cerebral structural organization



LATERAL TEGMENTAL
NORADRENALINE SYSTEM

SPECIFIC FUNCTIONS OF THE SAM-AXIS

Adipose tissue-----lipolysis (β-AR)
Adrenal medulla---secretion of catecholamines
Eye----------contraction radial muscle (α-AR)
relaxation ciliary muscle (β-AR)
Gall bladder----------relaxation (β-AR)
Heart----------increased cardiac output (β-AR)
Hair follicle----------contraction (α-AR)
Kidney----------increased blood pressure (α/β-AR)
Lacrimal glands----increased secretion (α-AR)
Liver----------increased blood sugar
Lungs----------bronchodilation (β-AR)
Pineal gland---------increased melatonin (β-AR)
Thyroid----------increased secretion
Micturition----------inhibited
Blood vessels-------vasoconstriction (α-AR)
Gastrointestinal-----delayed emptying (α/β-AR)

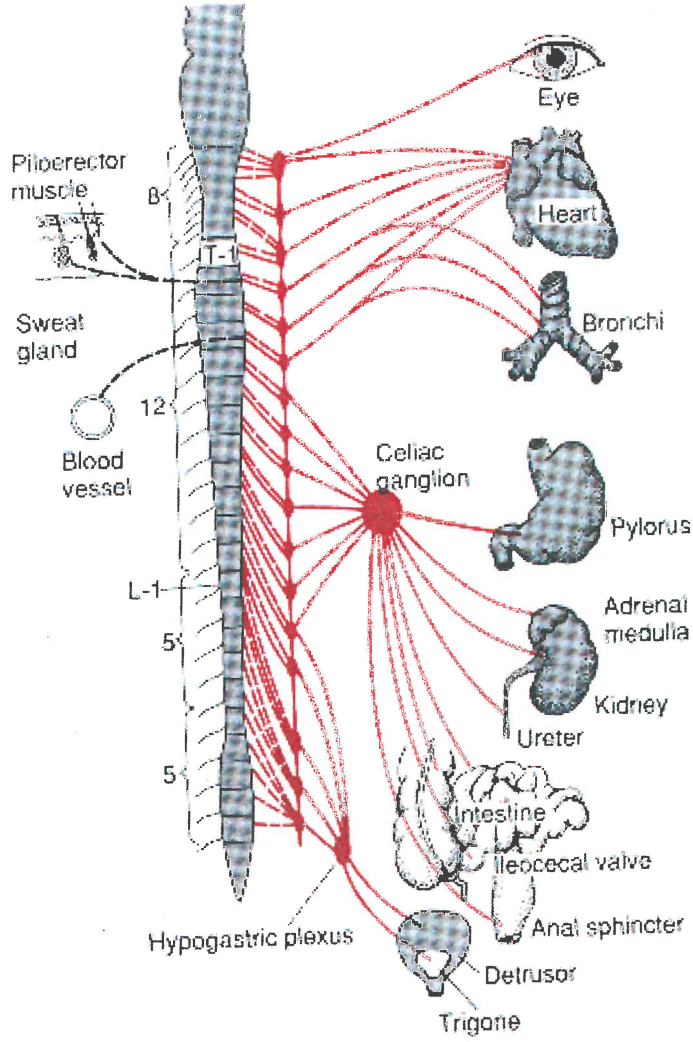


Figure 3.4 Functions of the CNA-system and the peripheral SAM-system

Legend to Figure 3.4

Figure 3.4: Functions of the CNA-system and the peripheral SAM-system.

(Compiled from 125, 126, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 149, 150, 151, 152)

[Figure 3.4 shows that the peripheral SAM-axis functions are, in general, to gear the body for action. The central noradrenergic (CNA) system seems, to a degree, to mirror these peripheral functions as the major behavioural effects are that of cerebral activation and increased adaptational plasticity. The specific effects on neurons, glial cells, blood flow and blood-brain barrier permeability underlie most of the behavioural functions and once again are mostly of an excitatory nature. It is easy to imagine how overexpression of these functions can lead to psychopathology.]

It is perhaps necessary to remind ourselves that the central noradrenergic system forms a major part of the ascending reticular activation system which consists of neuromodulatory networks such as the noradrenergic, serotonergic, cholinergic, histaminergic and dopaminergic systems (140). These networks are involved in the regulation of functions such as sleep, awakening, arousal, attention and wakefulness. The multiple projections from these neuromodulatory networks to various brain areas hint at the pervasiveness of their influence. This, in addition to the interconnectedness between the different neuromodulatory networks, and their regulation by the CRH system, emphasise the total integration of neural functions. The central role of the central nervous system CRH neurons and projections and their role in the integration of the stress response are discussed in Chapter 5.

3.4. Summary of the psychoneurological interactions in terms of the CNA/SAM-axis: A heuristic representation of the psychoneurological role of the system

The aim of this chapter was to demonstrate the bidirectional interaction between the psychological and biological aspects in terms of the central noradrenergic/ sympathoadrenomedullary axis. It therefore represents the psychoneurological part of the psychoneuroimmunological interaction as reflected by the CNA/SAM-axis. The first part dealt with evidence of the psychoneurological interaction in animals and the second part with that in man. Both confirmed the existence of a pervasive bidirectional psychoneurological interaction. The advantage of animal research is that the collection of certain types of physical evidence as well as experimental procedures considered unethical in man, are permissible in animals. Disadvantages do, unfortunately, also exist in animal experimental work - such as the problem of finer discrimination between certain psychological phenomena, as well as the legitimacy of extrapolation of the results to humans. However, a considerable bank of information exists which was originally derived from animal experimentation and eventually confirmed in man by indirect measures. It is clear that the functional and structural integrity of the CNA/SAM-axis has an influence on a multitude of behavioural functions and that many psychological disorders are characterised by abnormalities of the system. The psychological disposition

can, in turn, alter, not only the functionality of the CNA/SAM-axis, but also the biochemical and structural aspects as well as the genetic expression. Changes in the system as a result of controllable stressors can be seen as necessary adaptational processes, i.e., a form of noradrenergic plasticity. Stressors perceived as uncontrollable could, however, give rise to biological alterations that may cause, or predispose to psychopathology. It speaks for itself that the CNA/SAM-axis does not operate in isolation, or perhaps even as the major determinant of the behavioural functions mentioned, but as part of a large multiple receptor network. The major function of the CNA would in fact appear to be that of a neuromodulatory system which, through its projections to various areas of the brain, can influence the specific functions of those areas. The fact that the CNA system can exert an influence on other neuromodulatory systems such as the serotonergic, dopaminergic, cholinergic and other, is indicative of its diverse and pervasive influence on the behavioural functions. One would therefore expect concurrent, related or compensatory changes in interacting neural networks. Such a situation would make the identification of the primary neuromodulatory disturbance associated with a specific psychological function or disturbance extremely problematic. Several such concomitant alterations of the CNA system with other neuromodulatory systems were discussed. The interaction between the psycho- and the neurological can further not be described as simply bidirectional, but rather as a circuitry of reverberating influences. The continuation or discontinuation of mutual influences are probably determined by the nature of the feedback. This type of interaction where an emotional experience causes alteration in the physiological/anatomical integrity of the noradrenergic system, that in turn predisposes to shifts in the psychological disposition, which then lead to further functional or structural changes, makes coping, as well as adaptational sense.

The chapter is summarised in Figures 3.5 and 3.6. Figure 3.5 summarises the psycho-neurological interactions. Figure 3.6 shows the major central noradrenergic systems, their projections to other cerebral areas, neuromodulatory systems that interact with the noradrenergic system, the specific and psychological functions and disorders associated with the central noradrenergic system, as well as the bidirectional interaction between the psychological and the neural elements.

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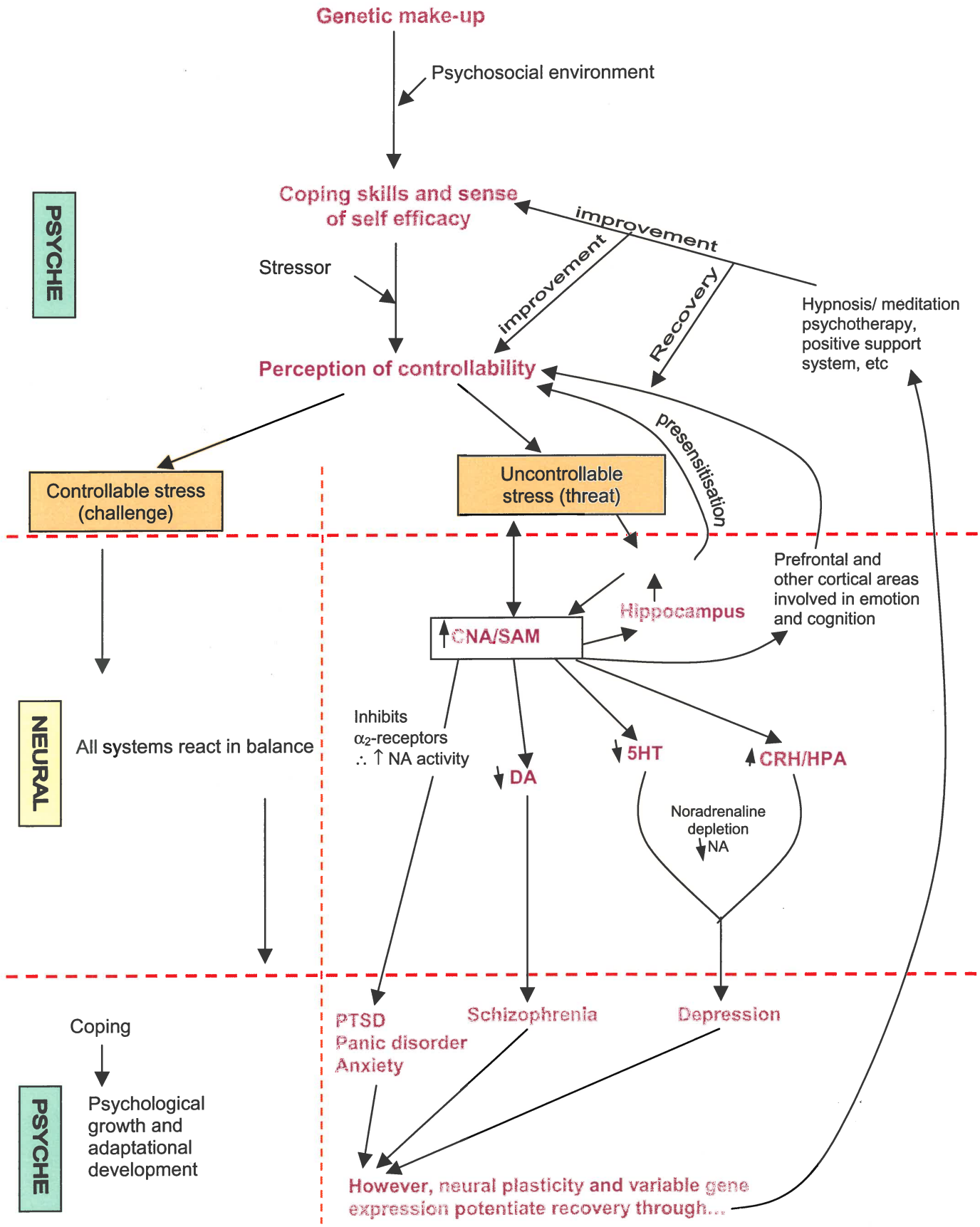


Figure 3. 5: Heuristic representation of the psychoneurological interactions in terms of the CNA/SAM-axis

Legend to Figure 3.5

Figure 3.5: A heuristic representation of the psychoneurological interactions in terms of the CNA/SAM-axis

[Figure 3.5 shows how the psychosocial environment acts in concert with the genetic make-up to produce an individual with specific coping skills and sense of self-efficacy. These qualities contribute to a large extent to the individual's perception of control in the face of stressors. Should a stressor be perceived as controllable all systems will react in balance and the end result would be a sense of coping, as well a psychological growth and adaptational development. Should the individual perceive the stressor as uncontrollable several events could take place – none of them mutually exclusive. The noradrenaline reserves of the brain may be depleted which could give rise to depression. Inhibition of the alpha-1adrenoceptors could give rise to conditions such as the post-traumatic stress syndrome, panic disorders or anxiety. Involvement of dopamine may lead to schizophrenia. It should be stressed that this was a scheme which evolved from studying the central noradrenaline system and therefore merely a representation of facts pertaining to the CNA/SAM-axis.]

SPECIFIC EFFECTS OF THE CENTRAL NORADRENERGIC SYSTEM ON THE BEHAVIOURAL FUNCTIONS AND ON MECHANISMS THAT INFLUENCE BEHAVIOURAL FUNCTIONS

Behavioural Functions

- facilitation of predatory attack behaviour
- improved acquisition and learning
- enhanced reactivity to stimulation
- augmented processing of sensory information
- accelerated motor responses
- augmented vigilance
- facilitation of arousal
- stimulation of the HPA-axis
- propagation and perpetuation of the stress response
- maintenance of non-spatial readiness to external cues
- augmentation of prefrontal cortex cognitive function
- involvement in the regulation of eating behaviour
- involvement in cerebral plasticity
- modulation of the induction of hippocampal synaptic plasticity

Specific effects on neurons

- altered excitability and neuronal information processing
- increased signal-to-noise ratio
- enhanced selectivity of target discharge, gating
- role in lactation-induced synaptic plasticity involving oxytocinergic somata
- modulation of central thyronergic activity
- activation of central second-messenger systems
- altered protein phosphorylation
- altered cerebral metabolism
- altered gene expression

Specific effects on astrocytes

- activation of second-messenger systems
- alterations in protein phosphorylation
- altered glycogen metabolism
- altered gene expression

General physiological and anatomical effects

- modulation of forebrain electroencephalographic activity
- increased cerebral blood flow
- increased cerebral metabolism
- altered blood-brain barrier permeability
- facilitation of structural organisation

BIDIRECTIONAL INTERACTION

EFFECTS OF PSYCHOLOGICAL EVENTS ON THE PHYSIOLOGICAL, BIOCHEMICAL AND ANATOMICAL INTEGRITY OF THE NORADRENERGIC SYSTEM

- Controllable stressors lead to transient as well as permanent adaptations which form part of normal development of coping skills
- Uncontrollable stress and perceptions of non-coping suppress adaptational changes and may predispose to later development of psychological disorders

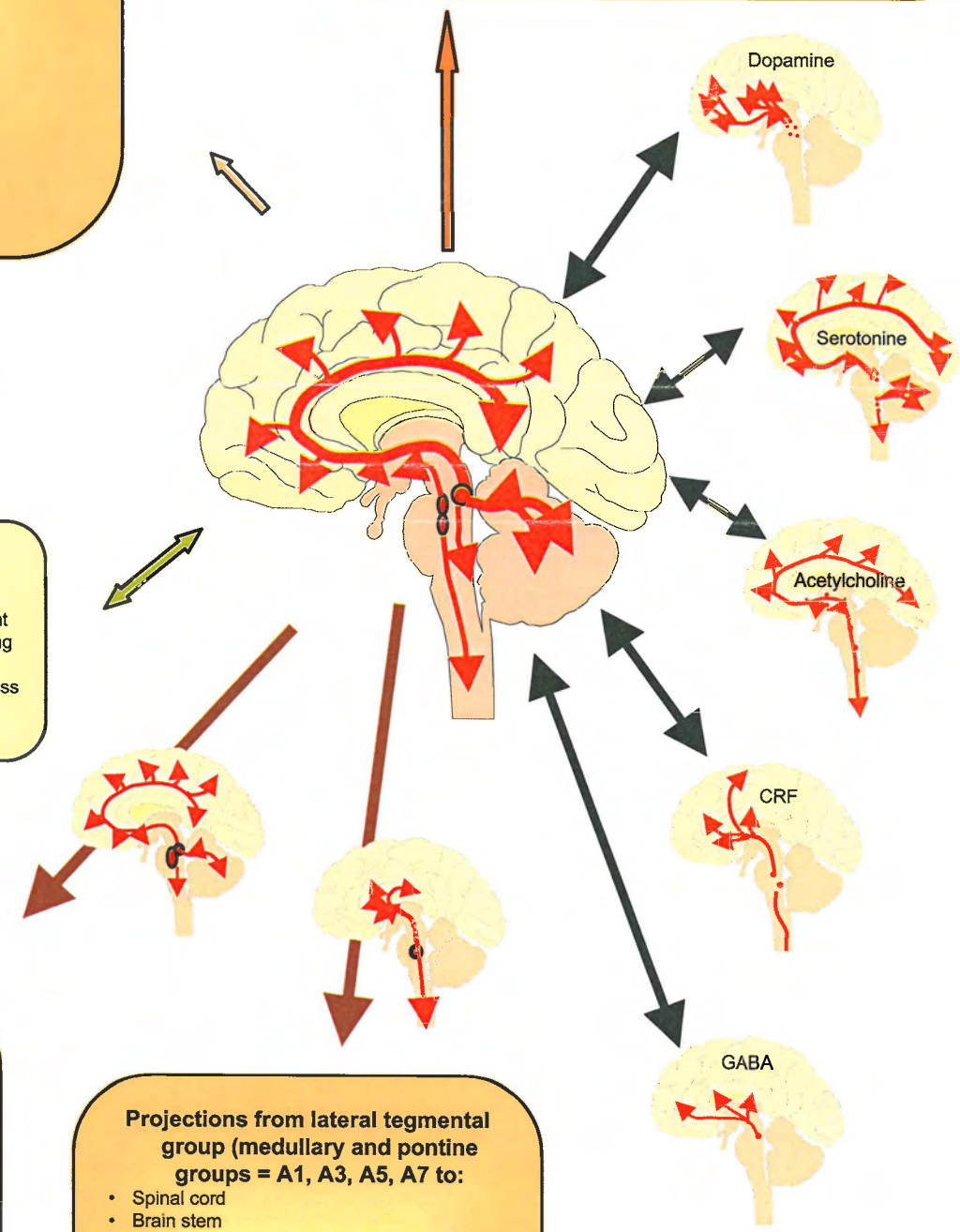
PSYCHOLOGICAL FUNCTIONS AND DISORDERS WITH VARIATIONS IN CENTRALNORADRENERGIC ACTIVITY

ASSOCIATED FUNCTIONS

Feeding
Grooming
Attack
Eating
Awakening
Inhibition of REM-sleep
Memory acquisition
Memory consolidation
Learning
Conditioning
Vigilance
Concentration
Recognition
Aggression
Anger
Fear
Pleasure
Helplessness
Defensiveness
Reward sensation
Panic
Resentment
Hostility
Coping
Self-efficacy
Emotional arousal
Non-specific stress response
Presensitisation to stress

ASSOCIATED DISTURBANCES

Attention-deficit / hyperactivity disorder
Conduct disorder
Tourette's disorder
Separation anxiety disorder
Alzheimers
Substance abuse
Alcohol dependence
Shizophrenia
Panic disorders
Generalised anxiety disorder
Phobic disorders
Obsessive compulsive disorder
Posttraumatic stress disorder
Eating disorders
Sleep disorders
Pathological gambling
Paraphilias
Borderline personality disorder
Sensation-seeking
Reward-dependence
Type A personality
Major depressive disorder
Bipolar disorders
Suicidal behaviour
Learned helplessness



THE MAJOR CENTRAL NORADRENERGIC SYSTEMS AND THEIR PROJECTIONS TO OTHER BRAIN AREAS

Projections from locus coeruleus group: (locus coeruleus and subcoeruleus) to:

- Spinal cord
- Brain stem
  Primary sensory nuclei of the somatosensory, auditory, gustatory and visual systems
- Hypothalamus
  All hypothalamic nuclei receive NA innervation, some from both projection groups
- Cerebellum
  Provides the primary NA input
- Thalamus
  Major input, to non-specific thalamic nuclei
- Basal forebrain
  Major source of NA innervation
- Hippocampal formation and amygdala
  Almost exclusive source of NA innervation
- Cerebral cortex
  Exclusive source of NA innervation. Two distinct populations of NA neurons:

a) localised arborisation in restricted areas of the cortex
b) markedly collateralised axons innervating widespread areas of the cortex

Projections from lateral tegmental group (medullary and pontine groups = A1, A3, A5, A7 to:

- Spinal cord
- Brain stem
  Raphe nuclei, cranial nerve motor nuclei, nuclei associated with the cerebellum
- Hypothalamus
  All hypothalamic nuclei receive NA innervation, some from both projection groups
- Cerebellum
  Small input to cerebellum
- Thalamus
  Innervation to isolated thalamic nuclei
- Basal forebrain
  Minor contribution to medial and lateral septal nuclei, nucleus of the diagonal band, nucleus accumbens, interstitial nucleus of stria terminalis, olfactory tubercle, anterior amygdaloid area, central nucleus of the amygdala, basolateral nucleus

INTERACTIONS BETWEEN THE CENTRAL NORADRENERGIC SYSTEM AND OTHER NEUROHORMONAL REGULATORY SYSTEMS, INCLUDING:

- DOPAMINERGIC,
- SEROTONERGIC,
- ACETYLCHOLINERGIC,
- CORTICOTROPIN-RELEASING HORMONE,
- GABA-ERGIC

Figure 3.6: A heuristic model of the psychoneurological relationship in terms of the central noradrenergic system

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Legend to Figure 3.6.

Figure 3.6: Central noradrenergic system in psychoneurological context.

[The figure illustrates the two major central noradrenergic systems, i.e., the locus coeruleus and the lateral tegmental groups of noradrenergic neurons (middle of diagram). It shows their projections to other cerebral areas (left bottom-half of picture), the neuromodulatory systems which interact with the noradrenergic system (right bottom-half), the specific mechanisms through which noradrenergic activity influences cerebral function (specific functions) (top-left), the psychological functions and disorders associated with the central noradernergic system (top-right), as well as the bidirectional interaction between the psychological and the neural elements (middle-left).]

In view of the multidisciplinary, integrative nature of the writing, the topic was dealt with in a fairly synoptic manner and a host of supporting evidence, as well as in-depth debating, had to be omitted from the chapter. The writing of a number of review articles that could considerably contribute to our understanding is suggested, including (tentatively suggested titles)

- The role of cerebral plasticity in the acquisition and extinction of adverse psychological patterns and psychiatric disorders
- Variable gene expression and psychological behaviour
- The mind-body paradigm in terms of the ascending reticular activating system neuromodulatory network.

In conclusion it can be said that the CNA/SAM-axis most likely exerts its diverse and pervasive influence on the behavioural functions predominantly through its role as a major neuromodulator. Behavioural influences can, in turn, alter the functional and anatomical integrity of the CNA/SAM-axis, depending on the perception of the controllability of the situation. As perception of controllability is dependent on alterable factors, such as coping skills and degree of self-efficacy, and, in view of the enduring plasticity of the CNA system, as well as the variability of the gene expressions, one could assume the possibility of psychosocial correction of similarly induced adverse neural structure and function. Surely, this must present a case for changing the argument of *nurture versus nature* into a plea to *nurture nature*.

This chapter demonstrated the psychoneurological interaction in terms of the CNA/SAM-axis. It showed that the central noradrenergic system primarily serves as neuromodulator and in this capacity acts in concert with all other modulator systems to set the psychological tonus. The next chapter will deal with the neuroimmmunological interactions in terms of the CNA/SAM-axis.

References

1. Petty F, Kramer G, Wilson L, Chae Y-L. Learned helplessness and *in vivo* hippocampal norepinephrine release. Pharmacol Biochem Behav 1993;46:231-235.

2. Depression and suicide. In: EP Seligman, DL, Rosenhan. Abnormality. WW Norton and Company, Inc., 1998, p246.

3. Bloom FE, Lazerson A. Emotions: The highs and the lows of the brain. In: Brain, Mind and Behaviour. 2nd edition. Freeman and Company, NY, 1996, p23.

4. Bremner JD, Krystal JH, Southwick SM, Charney D. Noradrenergic mechanisms in stress and anxiety. 1. Preclinical studies. Synapse 1996;23:28-38.

5. Grant SJ, Huang YH, Redmond DE. Benzodiazepines attenuate single unit activity in the locus coeruleus. Life Sci 1979;27:22-31.

6. Aston-Jones G. Behavioural functions of locus coeruleus derived from cellular attributes. Physiol Phsychol 1986;13:118-126.

7. Aston-Jones G, Shipley MT, Chovet G, Ennis M, van Bockstaele E, Pieribone V. Afferent regulation of locus coeruleus neurons: anatomy, physiology and pharmacology. In: CD Barnes and O Pomeiano, (eds). Progress in Brain Research, Elsevier Sci. Publ., 1991, pp 501-519.

8. Kopin IJ, Eisenhofer G, Goldstein D. Sympathoadrenal medullary system and stress. In: GP Chrousos, DL Loriaux and PW Gold, (eds). Mechanisms of Physical and Emotional Stress. Plenum Press, NY and London, 1988, pp11 - 23.

9. Bremner JD, Krystal JH, Southwick, Charney DS. Noradrenergic mechanisms in stress and anxiety: II. Clin Studies. Synapse 1996;23:39-51.

10. Barret JA, Shaikh MB, Edinger H, Siegel A. The effects of intrahypothalamic injections of norepinephrine upon affective defense behaviour in the cat. Brain Res 1987;426:381-384.

11. Rasmussen K, Jacobs BL. Single-unit activity of locus coeruleus neurons in the freely moving cat II. Conditioning and pharmacological studies. Brain Res 1986; 371:335-344.

12. Rasmussen K, Morilak DA, Jacobs BL. Single-unit activity of locus coeruleus neurons in the freely moving cat I. During naturalistic behaviors and in reponse to simple and complex stimuli. Brain Res 1986;371:324.

13. Levine ES, Litto WJ, Jacobs BL. Activity of cat locus coeruleus noradrenergic neurons during the defense reaction. Brain Res 1990;531:189-195.

14. Grant SJ, Redmond DE. Neuronal activity of the locus coeruleus in awake *Macaca arctoides*. Exp. Neurol 1984;84:701-708.

15. Redmond DE, Jr. New and old evidence for the involvement of a brain norepinephrine system in anxiety. In: Phenomenology and Treatment of Anxiety. Spectrum Publ., 1979, pp153-201.

16. Redmond D, Huang Y. New evidence for a locus coeruleus norepinephrine connection with anxiety. Life Sci 1979;25:2149-2162.

17. Aghajanian G. Tolerance of locus coeruleus neurons to morphine and suppression of withdrawal response by clonidine. Nature 1978;276:186-188.

18. Foote SL, Aston-Jones G, Bloom FE. Impulse activity of locus coeruleus neurons in awake rats is a function of sensory stimulation and arousal. Proc Natl Acad Sci USA 1980;77:3033-3037.

19. Aston-Jones G. The locus coeruleus: behavioural function of locus coereleus derived from cellular attributes. Physiol Psychol 1985;13:118-126.

20. Abercrombie ED, Jacobs BL. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats II. Adaptaion to chronically presented stressful stimuli. J Neurosci 1987;7:2844-2848.

21. Rosenzweig MR, Leiman AL, Breedlove SM. Learning and memory: Biological perspectives. In: Biological Psychology. (2nd ed). Sinauer Ass. Inc., Sunderland, Massachusetts, 1999, p519.

22. Rosenzweig MR, Leiman AL, Breedlove SM. Biological rhythms, sleep dreaming. In: Biological Psychology (2nd ed). Sinauer Ass. Inc., Sunderland, Massachusetts, 1999.

23. Bloom FE, Lazerson . Emotions: The highs and the lows of the brain. In: Brain, Mind and Behaviour (2nd ed). WH Freeman and company, NY, 1996, pp207-235.

24. Bloom FE, Lazerson A. Homeostasis: Maintaining the internal environment. In: Brain, Mind and Behaviour (2nd ed). WH Freeman and Company, NY, 1996 pp137-166.

25. Solomon Z, Garo K, Bleich A, Grupper D. Reactivation of combat-related posttraumatic stress disorder. Am. J. Psychiatry 1987;144:51-55.

26. Bremner JD, Southwick SM, Johnson DR, Yehuda R, Charney DS. Childhood physical abuse in combat-related posttraumatic stress disorder. Am J Psychiatry 1993;150:235-239.

27. Bremner JD, Charney DS. The anxiety disorders. In: Conn's Current Therapies. Raven Press, NY, 1994.

28. Davis M. Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. Behav Neurosci 1986;100:814-824.

29. Davis M. The role of the amygdala in conditioned fear. In: J. Aggleton (ed), The Amygdala, Neurobiological Aspects of Emotion, Memory and Mental Dysfunction. Wiley Liss. NY, 1992, pp225-306.

30. Selden NRW, Robbins TW, Everitt BJ. Enhanced behavior conditioning to context and impaired behaviour and neuroendocrine response to conditioned stimuli following ceruleo-cortical noradernergic lessions: Support for an attentional hypothesis of central noradrenergic function. J Neuro sci 1990;10:531-539.

31. Adell A, Garcia-Marquez C, Armario A, Gelpi E. Chronic stress increases serotonin and noradrenaline in rat brain and sensitises their responses to further acute stress. J Neurochem 1988;50:1678-1681.

32. Anisman H, Irwin J, Bowers W, Ahluwalia P, Zacharko RM. Variations of norepinephrine concentrations following chronic stressor application. Pharmacol. Biochem Behav 1987;26:653-659.

33. Nissenbaum LK, Zigmond MJ, Sved AF, Abercrombie ED. Prior exposure to chronic stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a novel stressor. J Neurosci 1991;11:1478-1484.

34. Joh TH, Gregham C, Reis D. Chemical demonstration of increased accumulation of tyrosine hydroxylase protein in sympathetic ganglia and adrenal medulla elicited by reserpine. Proc Natl Acad Sci USA 1973;70:2767-2771.

35. Angulo J, Printz D, Ledoux M, McEwen BS. Isolation stress increases tyrosine hydroxylase mRNA in the locus coeruleus and midbrain and decreases proenkephalin mRNA in the striatum and nucleus accumbens. Mol Brain Res 1991;11:301-308.

36. Mamalaki E, Kvetnansky R, Brady LS, Gold PW, Herkenham M. Repeated immobilization stress alters tyrosine hydroxylase, corticotropin-releasing hormone and corticosteroid receptor messenger ribonucleic acid levels in rat brain. J. Neuroendocrinol 1993;4: 689-699.

37. Velucci SV, Parrott RF. Expression of c-fos in the ovine brain following different types of stress, or central administration of corticotrophin-releasing hormone. Exp Physiol 1994;79:241-248.

38. Gizang-Ginsburg E, Ziff EB. Nerve growth factor regulates tyrosine hydroxylase gene transcription through a nucleoprotein complex that contains c-fos. Genes Dev 1990;4: 477-491.

39. Pavcovich LA, Cancela LM, Volosin M, Molina VA, Ramirez OA. Chronic stress induces changes in locus coeruleus neuronal activity. Brain Res Bull 1990;24: 293-296.

40. Nakamura S. Axonal sprouting of noradrenergic locus coeruleus neurons following repeated stress and antidepressant treatment. Progr Brain Res 1991;88: 587-598.

41. Stone E, Platt JE. Brain adrenergic receptors and resistance to stress. Brain Res 1982;237:405-414.

42. Stone EA, Stocky A. Platt J, Trullas R. Reduction of the cyclic adenosine 3'5' monophosphate response to catecholamines in rat brain slices after repeated restraint stress. J Pharmacol Exp Ther 1985;233:382-388.

43. Gannon M, EcEwen BS. Calmodulin involvement in stress- and corticosterone-induced down-regulation of c-AMP generating systems in brain. J. Neurochem 1990;55:276-284.

44. Tsuda A, Tanaka M. Differential changes in noradrenaline turnover in specific regions of rat brain produced by controllable and uncontrollable shocks. Behav Neurosci 1985;99:802-817.

45. Weiss JM, Goodman PA, Lossito BG, Corrigan S, Charry JM, Baily WH. Behavioral depression produced by an uncontrollable stressor: relationship to norepinephrine, dopamine and serotonin levels in various region of rat brain. Brain. Res. Rev 1981;3:167-205.

46. Lechin F, Van der Dijs B, Benaim M. Stress versus depression.[Review]. Prog. Neuropsychopharmacol. Biol Psychiatry 1996;20(6):899-950.

47. Hellhammer DH, Rea MA, Bell M, Belkien L, Ludwig M. Learned helplessness: Effects on brain monoamines and the pituitary-gonadal axis. Pharmacol Biochem Behav 1984;21:481-485.

48. Anisman H, Zacharko RM. Multiple neurochemical and behavioral consequences of stressors : Implications for depression. Pharmacol Ther 1990;46:119-136.

49. Anisman H, Zacharko RM. Depression as a consequence of inadequate neurochemical adaptation in reponse to stress. Br J Psychiatry 1992;160:36-43.

50. Minor RR, Pelleymounter MA, Maier SF. Uncontrollable shock, forebrain norepinephrine and stimulus selection during choice escape learning. Psychobiol 1988;16:135-145.

51. Weiss JM, Stone EA, Hanell N. Coping behavior and brain norepinephrine levels in rats. J. Comp. Physiol Psychol 1970;72:153-160.

52. Kitayama I, Yaga T, Kayahara T, Nakano K, Murase S, Otani M, Nomura J. Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. Biol Psychiatry 1997; 42(8):687-696.

53. Zafar HM, Pare WP, Tejani-Butt SM. Effect of acute or repeated stress on behavior and brain norepinephrine system in Wistar-Kyoto (WKY) rats. Brain Res Bull 1997;44 (3):289-295.

54. Stone EA, Zhang Y, John S, Filer D, Bing G. Effect of locus coeruleus lesion on c-fos expression in the cerebral cortex caused by yohimbine injection or stress. Brain Res 1993; 603:181-185.

55. Chrousos GP, Gold PW. The concept of stress and stress systems disorders. J Am Med Ass 1992;267:1244-1252.

56. Once more with feeling. In: J Le Doux. The Emotional Brain. Phoenix Paperback, London WC2H GEA, 1999, pp267-303.

57. Brain structures that mediate emotion. In: BT Donovan. Humors, Hormones and the Mind. MacMillan Press. London, 1988, pp211-219.

58. Kaufman PG, Nemeroff CB. Stress, neuropeptides and systemic disease. Acad. Press. Inc., NY, 1991, pp119-148.

59. Tassin JP, Lavielle S, Herve D, et al.. Collateral sprouting and reduced activity of the rat mesocortical dopaminergic neurons after selective destruction of the ascending noradrenergic bundles. Neurosc 1979;4:1569-1582.

60. Roth RH, Tam SY, Lda Y, Yang JS, Deutch AY. Stress and the mesocorticolimbic dopamine systems. Ann NY Acad Sci 1988;537:138-147.

61. Deutch AY, Clark WA, Roth RH. Prefrontal cortical dopamine depletion enhances the responsiveness of the mesolimbic dopamine neurons to stress. Brain Res 1990;521:311-315.

62. Deutch AY, Goldstein M, Roth RH. Activation of the locus coeruleus by selective stimulation of the ventral tegmental area. Brain Res 1986;363:307-314.

63. Imperato A, Puglisi-Allegra S, Casolini P, Angelucci L. Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary-adrenocortical axis. Brain Res 1991;538:111-117.

64. Arnsten AF. Catecholamine regulation of the prefrontal cortex. J Psychopharm 1997;11(2):151-62.

65. Sakanaka M, Shibasaki T, Lederis K. Distribution and efferent projections of corticotropin-releasing factor-like immunoreactivity in rat amygdaloid complex. Brain Res 1986;382:213-238.

66. Wallace DM, Magnuson DJ, Gray TS. The amygdala-brainstem pathway: selective innervation of dopaminergic, noradrenergic and adrenergic cells in the rat. Neuro Sci Lett 1989;97:252-258.

67. Magnuson DJ, Gray TS. Amygdala directly innervates parvocellular paraventricular hypothalamic CRF, vasopressin and oxytocin containing cells. [Abstract] Soc. Neurosci. 1988;14:1288-1291.

68. Mongeau R, Blier P, de Montigny C. The serotonergic and noradrenergic systems of the hippocampus, their interactions and the effects of antidepressant treatments. Brain Res Rev 1997;23:145-195.

69. Learning and memory. In: Brain, Mind and Behavior (2nd ed). Floyd E Bloom, Arlyne Lazerson. WH Freeman and Company. NY, 1996, p261.

70. Leon M. Catecholaminergic contributions to early learning. Adv. Pharmacol 1998;42:961-964.

71. Remembrance of emotions past. In: J Le Doux. The emotional brain. Phoenix paperbacks, London, 1998, p208.

72. Friedman M, Rosenman R. Type A behavior and your heart. Knopf, NY, 1974.

73. Palmero F, Codina V, Rosel J. Psychophysioloical activation, reactivity, and recovery in type A and type B scorers when in a stressful laboratory situation. Psychological Reports 1993;73:803-811.

74. Williams RB Jr, Suarez EC, Kuhn CM, Zimmerman EA, Schanberg SM. Biobehavioral Basis of Coronary-Prone behavior in middle-aged men. Part 1: Evidence for chronic SNS activation in Type A. Psychosom Med 1991;53:517-527.

75. Emotion. In: BT Donovan. Humors, Hormones and the Mind. MacMillan Press London, 1988, pp164-171.

76. Emotions: The highs and lows of the brain. In: FE Bloom, A Lazerson. Brain, Mind and Behavior (2nd ed). LWH Freeman and Co, NY, 1996, 216-218.

77. Boyce WT, Barr RG, Zeltzer LK. Temperament and the psychology of childhood. Pediatrics 1992;90(3):483-486.

78. Chrousos GP, Loriaux DL, Gold PW. (eds) Mechanisms of physical and emotional stress. Plenum Press, NY and London, 1988.

79. Arnsten AF, Steere JC, Jentsch DJ, Li BM. Noradrenergic influences on prefrontal cortical cognitive function: opposing actions at postjunctional alpha 1 versus alpha 2 adrenergic receptors. Adv Pharmacol 1998;42:764-767.

80. Gabel S, Stadler J, Bjorn J, Shindledecker R, Bowden CL. Sensation seeking in psychiatrically disturbed youth: relationship to biochemical parameters and behavior problems. J. Am. Acad. Child Adolesc. Psychiatry 1994; 33(1):123-129.

81. Garvey MJ, Noyes R jr, Cook B, Blum N. Preliminary confirmation of the proposed link between reward-dependence traits and norepinephrine. Psychiatry Res 1996; 65(1):61-64.

82. Bergh C, Eklund T, Sodersten P, Nordin C. Altered dopamine function in pathological gamling. Psychol Med 1997; 27(2):473-475.

83. Gabel S, Stadler J, Bjorn J, Shindledecker R. Homovanillic acid and dopamine-beta-hydroxylase in male youth: relationships with paternal substance abuse and antisocial behavior. Am J Drug Alcohol Abuse 1995; 21(3):363-378.

84. De Witte P. The role of neurotransmitters in alcohol dependence: Animal research. Alcohol Alcohol 1996;31 (Suppl 1):13-16.

85. Clayton CJ, Hicks RE. Ethanol, monoamines, and affect. J. Neural. Transm. Gen. Sect 1994; 98(3):169-195.

86. Kaplan HI, Sadock BJ, Grebb JA. Kaplan and Sadock's Synopsis of Psychiatry. Behavioral Sciences. Clinical Psychiatry. (7th ed). Williams and Wilkins. Baltimore, Maryland 21 202, USA, 1994.

87. Kavoussi R, Armstead P, Coccaro E. The neurobiology of impulsive aggression. Psychiatr Clin North Am 1997;20(2):395-403.

88. Figueroa E, Silk KR. Biological implications of childhood sexual abuse in borderline personality disorder. J Personal Disor 1997;11(1):71-92.

89. Arango V, Underwood MD, Mann JJ. Biological alterations in the brainstem of suicides. Psychiatr Clin North Am 1997;20(3):581-593.

90. Gilbert C. Major human cancers are preventable: Psychological stimuli induce a dopamine-thyroid-immune efficient mechanism. Psych Clin North Am 1997; 20(3):581-593.

91. Pirke KM. Central and peripheral noradrenaline regulation in eating disorders. Psychiatry Res 1996; 62(1):43-49.

92. McElroy SL, Pope HG Jr, Keck PE Jr, Hudson JI, Phillips KA, Strakowski SM. Are impulse-control disorders related to bipolar disorder? Compr Psychiatry 1996;37(4):229-240.

93. Pliszka SR, McCracken JT, Maas JW. Catecholamines in attention-deficit hyperactivity disorder: current perspectives. J. Am. Acad. Child Adolesc Psychiatry 1996;35(3):264-272.

94. Kafka MP. A monoamine hypothesis for the pathophysiology of paraphillic disorders. Arch Sex Behav 1997;26(4):343-358.

95. Krystal JH, Deutsch DN. Charney DS. The biological basis of panic disorder. J Clin Psychiatry 1996; 57 (Suppl l0):23-31(discussion 32-33).

96. Brawman-Mintzer O, Lydiard RB. Biological basis of generalized anxiety disorder. J Clin Psychiatry 1997; 58 Suppl 3:16-25 (discussion 26).

97. Southwick SM, Krystal JH, Bremner JD. Morgan CA, Nicolaou AL, Nagy LM, Johnson DR, Heninger GR, Charney DS. Noradrenergic and serotonergic function in posttraumatic stress disorder. Arch Gen Psychiatry. 1997;54(8):749-758.

98. Goddard AW, Charney DS. Toward an integrated neurobiology of panic disorder. J Clin Psychiatry 1997;58 Suppl 2: 4-11. (discussion 11-12).

99. Meas M, Minner E, Suy C, Vandervorst, Raus J. Coexisting dysregulations of both the sympathoadrenal system and hypothalamic-pituitary-adrenal-axis in melancholia. J Neural Transm [Gen Sect] 1991; 85:195-210.

100. Fritze J. The adrenergic-cholinergic imbalance hypothesis of depression: a review and a perspective. Rev neurosci 1993;4(1): 63-93.

101. Sulser F, Sanders-Bush E. The serotonin-norepinephrine link hypothesis of affective disorders: receptor-receptor interactions in brain. Av Exp Med Biol 1987;221:489-572.

102. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, Murburg MM, Ashleigh EA. Castillo S, Peskind ER. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. Arch Gen Psychiatry 1994;51(5): 411-422.

103. Potter WZ, Manji HK. Catecholamines in depression. An Update. Clin Chem 1994;40(2):279-287.

104. Maas JW, Katz MM, Koslow SH, Swann A, Davis JM, Berman N, Bowden CL, Stokes PE, Landis H. Adrenomedullary function in depressed patients. J Psychiatry Res 1994; 28(4):357-367.

105. Dinan TG. Noradrenergic and serotonergic abnormalities in depression : stress-induced dysfunction ?. J Clin Psychiatry 1996;57 (Suppl 4):14-81. [Abstract].

106. Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, Ordway GA. Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci 1997;17(21):8451-8458.

107. Mokrani MC, Duval F, Crocq MA, Bailey P, Macher JP. HPA axis dysfuntion in depression: correlation with monoamine system abnormalities. Psychoneuroendocrinology 1997; 22(Suppl 1):S63-68.

108. Kelly CB, Cooper SJ. Plasma noradrenaline reponse to electroconvulsive therapy in depressive illness. Br J Psychiatry 1997;171:182-186.

109. Arnsten AF, Steere JC, Hunt RD. The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical significance for attention - deficit hyperactivity disorder. Arch Gen Psychiatry 1996;53(5):448-455.

110. Carlsson A, Hansson LO, Waters N, Carlsson ML. Neurotransmitter aberrations in schizophrenia: new perspectives and therapeutic implications. Life Sci 1997; 61(2):75-94.

111. Palmer AM. Neurochemical studies of Alzheimer's disease. Neurodegeneration 1996; 5(4):381-391.

112. Goddard AW, Charney DS. Toward an integrated neurobiology of panic disorders. J Clin Psychiatry 1997; 58 suppl 2:4-11(discussion 11-2).

113. Fuxe K, Hokfelt T, Agnati LF, Johansson O, Goldstein M, Perez de la Mora M. Possami L, Tapia R, Teran L, Palacios R. Mapping out central catecholamine neurons: Immunohistochemical studies on catecholamine-synthesizing enzymes. In : Psychopharmacology : A Generation of Progress. MA Lipton, A Di Mascio, KK Killam, (eds), Raven Press, NY, 1978, pp67-94.

114. Sulser F. The serotonin-noradrenaline link-hypothesis of affective disorders. In: Psychiatry, vol 2, P. Pichot, P Berner , R Wolf and K Thau (eds). Plenum Publishing Corporation, 1985, pp411-416.

115. Sulser F, Conn PJ, Zawad JS, Sanders-Bush E. Molecular aspects of altered transmembrane regulation of the noradrenaline signal by antidepressants. Benzon Symposium on Drug Action, Copenhagen, 1996.

116. Goldberg D. A biosocial model for common mental disorders. Acta. Psychiart. Scand. 1994; 90 (suppl 385):66-70.

117. Miyake S. Factors influencing mental workload indexes. Sangyo Ika Diagaku Zasshi 1997;19(4):313-325.

118. Tache Y, Morley JE, Brown MR. Neuropeptides and stress (Hans Selye simposia on neuroendocrinology and stress) Springer-Verlag. NY, 1989.

119. Swann AC, Secunda SK, Koslow SH, Katz MM, Bowden CL, Maas JW, Davis JM, Robins E. Mania: Sympathoadrenal function and clinical state. Psychiatry Res 1991;37:195-205.

120. Gibbons JL. Endocrine disorders. In: HH Lader, (ed). Mental Disorders and Somatic Illness. Handbook of psychiatry (Vol 2). Cambridge Press, Cambridge, 1983, pp37-45.

121. Mitchell JP, Vulliet PR. Altered reactivity of the rat adrenal medulla following periods of chronic stress. Adv Exp Med Biol 221:367-374.

122. Mind modulation of the autonomic nervous system. In: Rossi ER (ed). The Psychobiology of Mind-Body Healing , Norton WW and company, NY, 1988

123. Bandura A. Catecholamine secretion as a function of perceived coping self-efficacy. J Consel Clin Psych 1980; 58(3):406-414.

124. McEwen BS. Hormones modulate environmental control of a changing brain. In: Comprehensive Human Physiology. R Greger and U Windhorst (eds) (Vol 1). Springer-Verlag, Berlin, 1996, pp473-493.

125. Schwartz JP. Development and plasticity. Overview. Adv Pharmacol 1998;42: 877-882.

126. Huether G. The central adaptation syndrome: psychosocial stress as a trigger for adaptive modifications of brain structure and brain function. Prog Neurobiol 1996;48:569-612.

127. Sorg O, Magistretti PJ. Characterization of the glycogenolysis elicited by vasoactive-intestinal-peptide, noradrenline and adenosine in primary cultures. Brain Res 1991;563:227-233.

128. Pape WP, Glavin GE. Restraint stress in biomedical research. Neurosci Biobehav Rev 1986;10:339-370.

129. Schasfoort EMC, DeBruin LA, Korf J. Mild stress stimulates rat hippocampal glucose utilization transiently via NMDA receptors as assessed by lactography. Brain Res 1988;475.

130. Eiring A, Hal Manier D, Bieck PR, Mowells RD, Sulser F. The "serotonin/norepinephrine link" beyond the β-adrenoceptor. Mol Brain Res. 1992;16:211-214.

131. Vaccarino FM, Hayward MD, Lee MW, Harigan DJ, Duman RS, Nestler EJ. Induction of immediate early genes by c-AMP in primary cultures of neurons from rat cerebral cortex. Molec Brain Res 1993;19:76-82.

132. Marshall KC, Christie MJ, Finlayson PG, Williams LT. Developmental aspects of the locus coeruleus noradrenaline system. Progr Brain Res 1991;88:173-185.

133. Boyeson MG, Krobert KA. Cerebellar norepinhephrine infusions, facilitate recovery after sensorimotor cortex injury. Brain Res Bull 1992; 29:435-439.

134. Levin BE, Dunn-Meywell A. Regulation of growth-associated protein 43 (GAP-43) m-RNA associated with plastic change in the adult rat barrel receptor complex. Molec Brain Res 1993;18:59-70.

135. Stone AA, Ariano MA. Are glial cells targets of the cerebral adrenergic systems ? Brain Res Rev 1989;14:297-308.

136. Bryan RMJ jr. Cerebral blood flow and energy metabolism during stress. Am J Physiol 1990;259:H269-H280.

137. Bryan RM, Lehmann RAW. Cerebral glucose utilization after aversive conditioning and during conditioned fear in rat. Brain Res 1988; 444:17-24.

138. Nathanson JA. Adrenergic receptors in brain microvessels. Trends. Neurol Sci 1983; 4: 422-424.

139. Ohata M, Takei HO, Fredericks WR, Rapoport SJ. Effects of immobilization stress on cerebral blood flow and cerebrovascular permeability in spontateously hypertensive rats. J Cereb Blood Flow Metab 1982;2:373-379.

140. Windhorst U. Bilateral organisation of the brain. In: Comprehensive human physiology. R Gregor and U Windhorst (eds) Vol 1. Springer-Verlag Berlin, 1996, pp1137-1160.

141. Partonen T. Possible pathophysiological mechanisms regulating food intake in seasonal affective disorder. Med Hypotheses 1996; 47(3):215-216.

142. Huang QH, Takaki A, Arimura A. Central noradrenergic system modulates plasma interleukin-6 production by peripheral interleukin-1. Am J Physiol 1997; 273:R731-738.

143. Witte EA, Marrocco RT. Alteration of brain noradrenergic activity in rhesus monkeys affects the alerting component of overt orientating. Psychopharmacol 1997;132(4):315-323.

144. Dratman MB, Gordon JT. Thyroid hormones as neurotransmitters. Thyroid 1996; 6(6):639-647.

145. Arnsten AF, Steere JC, Hunt RD. The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical significance for attention - deficit hyperactivity disorder. Arch Gen Psychiatry 1996;53(5):448-455.

146. Berridge CW. Modulation of forebrain electroencephalographic activity and behavioral state by the locus coeruleus - noradrenergic system: involvement of the medial septal area. Adv Pharmacol 1988;42:744-748.

147. Hasselmo ME, Linster C, Patil M, Cekic M. Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. J Neurophysiol 1997;77(6):3326-3339.

148. Katsuki H, Izumi Y, Zorumski CF. Noradrenergic regulation of synaptic plasticity in the hippocampal CA1 region. J Neurophysiol 1997;77(6):3013-3020.

149. Michaloudi HC, Mjboudi M, Poulain DA, Papadopoulos GC, Theodosis DT. The noradrenergic innervation of identified hypothalamic magnocellular somata and its contribution to lactation-induced synaptic plasticity. J Neuroendocrinol 1997; 9(1):17-23.

150. Rorig B, Sutor B. Regulation of gap junction coupling in the developing neocortex. Mol Neurobiol 1996; 12(3):225-249.

151. Bhatia SC, Saha S, Manchanda SK, Nayar U. Role of midbrain ventro-lateral tegmental area (VYTA) adrenergic mechanisms in facilitation of hypothalamically-induced predatory attack behaviour. Indian J Exp Biol 1997;35(4):332-337.

152. Holets VR. Anatomy and function of noradrenaline in the mammalian brain. In: The Pharmacology of Noradrenaline in the Central Nervous System. Oxford University Press, 1990, pp1-27.

CHAPTER 4

THE NEUROIMMUNOLOGICAL INTERACTION IN TERMS OF THE CNA/SAM-AXIS

The noradrenergic system, as one of the two major stress systems, consists, as was seen in the previous chapter, of the central noradrenergic system (CNA-system) and the peripheral sympathoadrenomedullary system (SAM-axis). In this writing the abbreviation CNA/SAM-axis will be used in referring to the noradrenergic system as a whole. In the previous chapter it was shown that activation of the central noradrenergic system and its sympathoadrenomedullary outflow are involved in many behavioural functions and is a feature of almost all arousal states, including physical, emotional and cognitive stress. It has further been linked to a variety of psychological/psychiatric disorders. The aim of this chapter is to provide evidence for the bidirectional interaction between the noradrenergic system and the immune system. This chapter thus represents the neuroimmunological aspects of the psychoneuroimmunological interaction in terms of the CNA/SAM-axis.

Introduction

Despite a vast amount of research on the interaction between the immune system and the noradrenergic system, confusion still prevails. This makes the field rather inaccessible to psychiatrists and physiologists alike. In order to arrive at a relatively rational conclusion, literally hundreds of publications had to be scrutinised. Reductionistic strategies were therefore employed in an attempt to present a simple heuristic representation of the interaction between the immune system and the CNA/SAM-axis. Reductionistic strategies employed included a) presentation of supporting evidence in table, rather than in descriptive format, b) short general discussions, based on the contents of the tables, without superfluous duplication of reference to authors, c) omission, where applicable, of the names of original authors, in favour of review authors, and d) a final summary of the chapter in the form of a schematic presentation of the neuroimmunological interaction in terms of the CNA/SAM-axis. For logistic reasons the immune system is subdivided into the primary lymphoid organs, the secondary lymphoid organs, and the

circulating immunocompetent cells and *in vivo* immunity.

This chapter contains a condensation of what would normally be spread over several chapters. As in the previous chapter a small-scale version of the final schematic integration is presented at the beginning of the chapter (Figure 4.1). The normal size version of Figure 4.1 is presented at its rightful place at the end of the chapter, as Figure 4.4. Presenting the final figure at the beginning of the chapter once again gives the reader, not interested in the detail, the opportunity to get an insight into the bidirectional interaction by merely looking at the final scheme.

The subdivisions include:

Figure 4.1 is presented on the next page, followed by the legend to Figure 4.1 on the subsequent page.

NORADRENERGIC ACTIVITY and IMMUNITY

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

he immune system on the noradrenergic activity

Effects on immune system

IN VIVO IMMUNO - REACTIVITY

SECONDARY LYMPH ORGANS

PRIMARY LYMPH ORGANS

PHYCHOSOCIAL DISPOSITION

THYMIC EFFECT ON NORADRENERGIC FUNCTION AND NORADRENERGIC CONTROL CENTRES

1. Necessary for development of neuro-secretory function during early development
2. Maintenance of adrenoceptor density
3. Regulation of adrenoreceptor responsiveness
4. Neuroregulatory effects through thymus-derived cytokines (IL-1, IL-3, MCSF, etc.), thymus-derived hormones (prolactin, ADH, oxytocin, tachykinins etc.) and thymic peptides
5. Behaviour effects include increase in spontaneous behaviour, suppression of anxiety and increased resistance to stress

NORADRENERGIC EFFECT ON SECONDARY LYMPHOID ORGANS (SPLEEN)

1. Involved in prenatal splenic development
2. Regulates splenic perfusion
3. Regulates lymphocyte and granulocyte release from lymphoid tissue in a blood-flow dependent and independent manner
4. Direct role in lymphocyte trafficking, antigen processing and presentation as well as cytokines production
5. Essential for immunocompetence but curtails excessive immunological reactivity
6. Generally immunosuppressive, but may be immune-enhancing, dependent on receptor type, stimulus intensity and duration as well as general immunological status
7. Dual effect within same immunological reaction with stimulation in the inductive phase and inhibition in the effector phase
8. B_2-adrenoceptor-cAMP-protein kinase activity inhibits pro-inflammatory pathway and stimulates anti-inflammatory pathway through differential effects on TH1 and TH2 cells. Can shift immune response from cellular to humoral

NORADRENERGIC EFFECT ON BONE MARROW

Role in perfusion, cellular migration and leukocyte release

BONE MARROW

NORADRENERGIC EFFECTS ON THYMUS

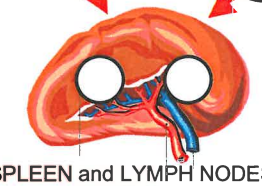
1. Regulatory function in thymus perfusion and release of cells from thymus
2. Necessary for early post-natal development, including thymocyte differentiation and receptor expression
3. Controls thymic micro-environment by influencing intra-thymic neurohormonal and peptidergic secretion
4. Essential for thymus-dependent immunological competence
5. Involved in thymus involution
6. Controls stimulus responsiveness of cells
7. Controls excessive immunological responses
8. May be a factor in gender-dependent differences in immunological responsitivity through interaction with steroid hormones

THYMUS

Thymosins
Thymopeptins
Thymulin
Cytokines
Tachykinins
Neurohypophysial hormones

B-cells

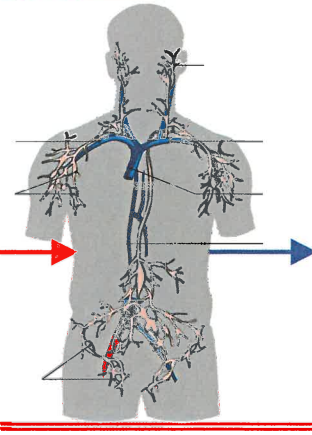
T-cells



SPLEEN and LYMPH NODES

NORADRENERGIC EFFECT ON IN VIVO IMMUNOREACTIVITY

1. Beta-adrenoceptors are found on lymphocytes, monocytes granulocytes and macrophage
2. Alpha-adrenoceptors are found on some immune cells and on vasculature (important in cell traffic and release)
3. Most phagocyte functions appear to be suppressed by NA
4. Essential for T-cell response (cytotoxic T-cell activity, Con A-induced proliferation, IL -2 production, IL -2 receptor expression, T-cell dependent antibody response) but control excessive reactivity
5. Tonic inhibition of tumoricidal activity (NK-cell activity etc) and T-independent antibody responses (polyclonal B-cell responses)
6. Inhibition of macrophage antigen presenting activity
7. Immunological effects of NA stimulation are dependent on receptor type and density, intensity and duration of stimulation as well as on stage of immunological reaction and immunology status
8. Effects on immune responses influence cytokine production
9. Helps to localize inflammatory response
10. Protects body from the tissue damage inflicted by overproduction of systemic proinflammatory cytokines
11. Stress-induced adrenergic stimulation may expose the body to infectious complications and autoimmune diseases and tumour growth
12. Hypoactivity may predispose to fibromyalgia/chronic fatigue syndrome



EFFECTS OF THE IMMUNE SYSTEM ON NEUROLOGICAL FUNCTION.

1. Sensory function
2. Affects neuronal firing rate
3. Affects rate of noradrenaline secretion and stimulates adrenoceptor expression
4. Regulatory feedback through immunocompetent cell-derived cytokines, neuro-endocrine and peptidergic substances
5. Possible antibody – induced cerebral effect
6. Stimulation of the central stress response with a basal tonic inhibitory effect on stress-related behaviour

SUMMARY OF NEUROIMMUNOLOGICAL INTERACTION EFFECTS OF NORADRENERGEC ACTIVITY ON IMMUNITY

1. Necessary for immunodevelopment and immunocompetence
2. Major factor in immunorestraint
3. Essential for self-tolerance (basal tonic inhibitory effect helps to curtail auto-immune reactivity)
4. Opposite effects with acute (enhancement) and chronic (suppression) hyperstimulation
5. Variations in noradrenergic activity implicated in tumourgenesis, chronic inflammatory disorders, stress-induced Immuno-incompetence and allergies
6. Implicated as a factor in the immune alterations obtained through conditioning and in immune alterations with drug abuse

EFFECTS OF THE IMMUNE SYSTEM ON NORADRENERGIC ACTIVITY

1. Necessary for neurosecretory development and maintenance of adrenoceptor expression and functional integrity
2. Acts as sensory system to alert CNS about peripheral infectious and immunological occurences
3. Immunologically-derived cytokines give rise to the central stress response through induction of stress hormone secretion
4. (HPA-axis and CNA/SAM-axis) and inhibition of anti-stress hormones (GH, LH, FSH etc)
5. Immunologically-derived cytokines implicated in behavioural effects such as sickness behaviour, mood changes, sleep, eat and locomotor disturbances, anxiety, as well as exploratory, coping and related behavioural phenomena
6. Excessive immunological inflammatory activity may predispose to psychological disorders
7. Cytokine therapy can have neurotoxic effects partially mediated via central NA system

Figure 4.1: A schematic representation of the bidirectional interaction between the CNA/SAM-axis and the immune system

Legend to Figure 4.1

Figure 4.1: A schematic representation of the bidirectional interaction between the CNA/SAM-axis and the immune system.

[On the left hand side of the diagram the effect of the CNA/SAM-axis on the primary lymphoid organ (thymus and bone marrow) immunity, the secondary lymphoid organ (spleen and lymph nodes) immunity, and on *in vivo* immunological reactivity and competence are shown. The right hand side represents the effects of the immune system on the functional and developmental aspects of the CNA/SAM-axis. At the bottom of the page the overall effects are summarised.]

4.1 Bidirectional interaction between the CNA/SAM-axis and the primary lymphoid organs

4.1.1 Effect of the CNA/SAM-axis on the primary lymphoid organs.

Its as yet impossible to be dogmatic about the interaction between the CNA/SAM system and the primary lymphoid organs, as

- the results of *in vitro* tests do not represent a good reflection of occurrences in the *in vivo* environment
- a multitude of factors influence the microenvironment, and by implication the functional integrity, of the primary lymphoid organs
- the interaction is dependent on the chronological order of neural and immune stimulation,
- previous immunological sensitisation, and on the duration of the heightened noradrenergic stimulation
- across-species extrapolation of results may sometimes lead to confusion

Investigating the effect of adrenergic function on the vascular and blood flow behaviour of the thymus is fairly simple in comparison to that on the cellular elements. This is especially true when referring to the mechanisms of negative and positive selection of T-cells, which form part of the differentiation process of bone marrow derived thymic cells. Maturation and differentiation of thymic cells are known to be influenced both by extra-thymic neuroendocrine factors and by the microenvironment of the thymus itself. The microenvironment of the thymus is however, also affected by the neuroendocrine regulatory mechanisms. The regulatory role of neuro-endocrinological substances on the thymocytes, be it direct or through an influence on the microenvironment, is a two-way street as humoral substances from the thymus are in turn able to influence extra-thymic endocrine secretion. These interactions are touched upon in the following paragraphs.

The microenvironment of the thymus is largely a product of the secretory ability of the thymic epithelial cells, and of the cellular interactions mediated through adhesion molecules and membrane receptors (1). Cell-to-cell interactions are probably also regulated by humoral factors. The epithelial cells of the thymus are known to secrete:

- peptide hormones such as the thymosins, thymopeptin and thymulin (1,2,3). Thymosins, such as thymosin-α_1, thymosin β_4 and thymosin factor 5, exert functions such as the induction of lymphopoiesis, stimulation of T-cell maturation, maintenance of T-cell reactivity as well as augmentation of mitogen responses, alloreactivity and lymphokine production (4,5).
- cytokines such as interleukin-1, interleukin-3, interleukin-6, as well as the granulocyte macrophage colony stimulating factor, (6,7,8)
- intracellular matrix proteins, including type IV collagen, laminin and fibronectin (9) and probably a number of hormones not generally associated with the thymus, such as prolactin, antidiuretic hormone, and oxytocin (1,10). Thymic epithelial cells are said to synthesize neuroendocrine-related peptides belonging to the 3 neuroendocrine families i.e. the neurohypophysial, the tachykinin and the insulin families (11).

The above factors all contribute to the microenvironment of the thymus - directly as well as indirectly through their effects on thymocyte proliferation, maturation and differentiation and thus by implication, to thymic immune function.

The secretory function of the thymic epithelial cells, and therefore the micro- environment of the thymus, is further known to be influenced by the so-called developmental hormones of the circulation, such as the thyroid hormones, insulin, glucocorticoids, growth hormone and prolactin. Evidence for their role in thymic function is seen in

- the expression of their receptors on thymic epithelial cells
- their modulation of thymic hormone secretion, of cytokeratin expression and of cellular proliferative processes (12,2)
- in patients with hormonal disturbances where the stimulatory effects of hormones such as the thyroid hormones, insulin and growth hormone are borne out by changes in thymic hormone levels in patients with hypopituitarism, acromegaly, hyper- and hypothyroidism, low T_3 syndromes and in patients with type 1 diabetes mellitus (10).

Prolactin is perhaps the major neurohypophysial hormone with regard to thymic function. Prolactin has even been suggested to be the determining factor in thymic immunological competence (1).

Immunohistochemical studies further demonstrate an abundancy of peptidergic innervations and peptidergic receptors in the thymus and indications are that neuropeptidergic modulation is involved in alterations of the immune response (13,14,8). Reported thymus-associated peptidergic activities include vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP) and substance-P (SP). The existence of co-localisation of various transmitter substances within a single nerve fibre has also been reported. In view of co-localised monaminergic and peptidergic transmitter substances, such as noradrenaline and substance P, a functional modulatory co-operation is suggested between the sympathetic nervous system and the influence of peptide hormones on thymic immune function. This presents yet another confounding factor in the attempt to define the role of one single influence, such as the noradrenergic system, on primary lymphoid organ immunity.

Publications dealing with the effects of the CNA/SAM system on thymus immune function are summarised in Table 4.1. The results of various workers are presented in table form in an attempt to gain some insight into this field, where a marked degree of confusion still exists.

Table 4.1 : Noradrenergic influence on primary lymphoid organs

ORGAN	INNERVATION	TECHNIQUE	FUNCTIONAL IMPLICATIONS	REFERENCES
BONE MARROW	Myelinated and unmyelinated fibres in bone marrow	Light and electron microcopy	Innervation of bone marrow	Calvo, 1968 (15)
	Fibres found in association with vascular plexuses and marrow substance	Fluorescence microcopy	Possible role in hemopoiesis and cell migration through blood flow effects	Felten et al, 1985; Felten and Felten 1991 (16,17)
	Innervation of bone marrow starts late in foetal life - just before the onset of haemopoietic activity	Microscopy	May be involved in blood flow, cellular migration and release	Calvo & Haas, 1969; Miller & McCuskey, 1973 (18,19)
	Nerve endings among lymphopoeitic and haemopoietic cells and along vasculature	Immuno-histochemistry	Possible influence on haemopoiesis and perfusion	Gibson-Berry et al, 1993 (20)
	Sympathectomy and a_1-adrenergic antagonist increase peripheral blood leukocyte count	Chemical sympathectomy with 6- hydroxydopamine	A role for NA innervation in thymic perfusion and leukocyte release	Maestroni et al, 1992 (21)
	Controversy as to whether sympathetic fibres have any synapses with cells, and thus any direct influence on cell development and release	Silverstaining Falck – Hillarp histofluorescence	Speculation that effects on cell release may be secondary to effect on peripheral resistance or effect via volume transmission	Takase and Nomura 1957; Muller and McCuskey 1973; De Pace and Webber, 1975 (22,19,23)
	NA release mobilizes fat from the marrow			Tran et al, 1987 (24)
	Prozasin (a_1-antagonist) increases peripheral leukocyte count and may possibly increase myelopoiesis. Same effect with chemical sympathectomy	Pharmacological manipulation with prozasin and with 6-hydroxydopamine	May be just a blood flow phenomenon	Maestroni et al, 1992 (21)
THYMUS	The thymus can correct the brain alpha and beta-adrenoceptor decrease in density which occurs in old age	Neonatal thymus graft	There is a two-way effect between CNS and thymus. Thymus supports CNS receptor density	Rossolini et al, 1991 (25)

Mature thymocytes (= cortisone resistant) express twice the number of beta-adrenoceptors per cell as immature (cortisone sentitive) thymocytes	Ligand binding studies	Innervation, as for the thymus as a whole, increases with maturation	Fuchs et al, 1988; Bach 1975 (26,27)
NA innervation predominantly vascular in early development. Vascular innervation increases with growth	Electron microscopy; Fluoressence immunochemistry	A role in thymic perfusion	Bulloch and Pomerantz, 1984; Ackerman et al, 1991, Singh, 1984; Williams and Felten 1981 (28,29,30,31)
NA innervation of the thymic parenchyma is predominantly a post -natal occurence	Fluorescence histochemistry	Suggests a very low or no role of the NA system in foetal development	Ackerman et al, 1991; Bellinger et al, 1992 (29,8)
The cortical zone is the first parenchymal area to be innervated followed by a dramatic increase in the innervation of the corticomedullary junction	Fluorescence histochemistry		Ackerman et al, 1991 (29)
NA fibres to the thymus are derived predominantly from post ganglionic cell bodies of the superior cervical ganglion and stellate ganglion	Fluorescence histochemistry	Confirmation of sympathetic nervous system innervation of thymus	Bulloch and Pomerantz, 1984; Tollefson and Bulloch, 1990 (28,32)
In the adult a network of NA fibres in association with blood vessels, arterial and venous plexuses, intralobular septa and distributed amongst thymocytes of subcapsular, corticals cortico-medullary and medullary parenchyma. Cortical parenchyma (immature thymocytes) well innervated. Cortico-medullary boundry (important for thymocyte emigration) densely innervated. Peak parenchymal density occurs after involution. Increase in embryogenic innervation matched by an increase in thymic NA concentration. Noradrenergic supply to medulla limited mainly to bloodvessels	Ultra structural microscopy, Fluorescence histochemistry, TH^+ immunocytochemistry. Liquid chromatography with electrochemical detection (HEC)	A role for NA in vascular resistance, blood flow and perhaps thymocyte migration, within as well as from the thymus A possible role for NA in thymocyte proliferation and maturation Peak density after involution may merely reflect the decrease in thymic size	Ackerman et al, 1991; Bellinger et al, 1988; Bellinger et al, 1990; Felten et al, 1985; 1987; Williams and Felten, 1981; Williams et al, 1981; Felten & Felten 1991; Madden et al, 1995; Bulloch et al, 1987 (29,33,14,16,31, 34,13,35,36)
Thymocytes in early developmental stages demonstrate higher cAMP responses to NA stimulation than that during later developmental stages	Equilibrium binding assays	May be a role for NA in early cellular developmental processes OR a function of lower receptor density and NA availability	Singh,1979 (37)
Thymocyte maturation is accompanied by an increase in ß-adrenoceptor density (especially in cortex and paracortex) and a decrease in 2nd messenger responsiveness to NA stimulation	Equilibrium binding studies LCEC for monoamines	May be a role for NA in differentiation of thymic cells. May be a functional down/up regulatory mechanism	Bellinger et al, 1989; Ackerman et al,1991; Fuchs et al,1988; Bach, 1975 (38,29,26,27)
Mature spleen cells show a smaller cAMP response to isoproterenol than mature adult stage thymocytes	Equilibrium binding studies	Possibly further prove of a decreased responsiveness with maturation. or of a up/down regulatory mechanism due a change in receptor density of NA c oncentration	Bach 1975 (27)
NA fibres are maintained with aging - accompanied by an increase in thymic NA concentration. An appearance of hyperinnervation with thymic involution	Fluorescence histochemistry. LCEC for monoamines	May be secondary to thymic involution (thymus thus shows slower NA fibre development but more prominent maintenance of fibres in adulthood than secondary lymphoid organs	Ackerman et al, 1991 (29)
ß-adrenergic receptors shown on thymocytes	Mostly receptor-ligand binding assays	Indicates a role for sympathetic system in immunity	Fuchs et al, 1988; Singh 1979; Singh, 1984; Singh and Owen,1976; Singh et al, 1979 (26,37,39,40)
Rat thymus contains predominantly $ß_2$-adrenoreceptors (78%). Upregulation is seen under influence of sex steroid hormones	Radio-ligand binding studies	Suggests gender associated NA modulation of cell mediated immune responses. Could be of significance in gender-dependent immune responses	Marchetti et al, 1990 (41)

Thymic $ß_2$ adrenergic receptors show a clear sexual dimorphism in receptor organization during sexual maturation. Receptor density decreases with castration and increases when castrated rats receive oestradiol	Autoradiography	$ß_2$-adrenoreceptors density in the thymus is modulated by steriod hormones through transcriptional control of $ß_2$-adrenoceptor gene expression	Marchetti et al, 1990; Marchetti and Labrie 1990 (42,43)
Adrenaline increases thymocyte proliferation into the metaphase in a time and concentration dependent fashion	Tissue culture preparation	Suggests increased proliferation with B_2 -stimulation (The process is stimulated by phosphodiesterase inhibitors)	MacManus et al, 1971 (44)
Increases in intracellular cycle AMP augments differentiation and maturational marker expression (Thy-1) of thymic stem cells. This process is modulated by thymic hormonal factors. May act synergictically with thymopoeitin	Tissue culture preparations	cAMP promotes cellular maturation and proliferation. NA raises cAMP concentration and would thus by implication stimulate differentiation and maturation	Scheid et al, 1973; Scheid et al, 1975; Singh and Owen,1975; Singh and Owen, 1976 (45,46,47,39)
Thymus-dependent immune function and hormonal activity is suppressed in the absence of NA innervation	Thymic grafts	NA necessary fot T-cell dependent immune function	Bulloch et al, 1987 (36)
Severence of the sympathetic supply to the thymus suppresses the proliferative response to footshock and mitogens	Surgical sympathectomy	NA stimulation necessary for thymic proliferative response to stimulation in adult rodents	Wan et al, 1993 (48)
Chemical denervation of the thymus supports thymocyte proliferation in the thymic cortex but induces weight loss and apoptosis of the thymus	Chemical denervation with 6-hydroxydopamine or quanethidine	Suggests that NA inhibits cellular proliferation in thymus. Secretion of other humoral factors are however also suppressed by 6-hydroxydopamine	Kendall-Al-Shawaf, 1991 (49)
NA innervation suppresses thymocyte proliferation and differentiation in grafts	Foetal thymic transplantation (may represent chronic effect)	Sympathetic system suppresses proliferation and inhibits differentiation	Singh, 1985a; Singh,1985b (50,51)
Neuropeptide Y associated with NA fibres	Microscopy	Perhaps a functional modulation of NA function by neuropeptide Y	Kendall and Al-shawaf, 1991 (49)
The immune response induces marked time dependent changes in ß-adrenoceptor numbers and distribution as well as in the cAMP response	Radio-ligand binding studies, Autoradiography Northern blot	The NA activity should always be interpreted in the light of any antigenic stimulation as it may trigger an up of down regulation of $ß_2$-gene expression	Morale et al, 1992 (52)
Acute immobolization stress increases $ß_2$-adrenoceptor binding sites on thymocytes in a time-of-stress-application dependent manner. Chronic stress does not show the same effects	[3H] - DHA specific binding	Result of receptor density should be analysed as a function of psychological state and exposure time	Kuberu et al, 1992 (53)
Restoration of $ß_2$-adrenergic responsiveness in the brain of old mice and of young athymic mice	Neonatal grafts. Thymic extract (TME) administration	Some humoral thymic factor affects adrenergic Receptor responsiveness	Rossolini et al, 1991 (54)
The thymic extract (TME) modifies the isoproterenol- induced increase in submandibular gland and brain cortex DNA synthesis. TME increases a_1-adrenoceptor density	Grafts, TME administration	Some thymically- derived molecules can increase α_1-adrenoceptor density	Basso et al, 1994; Rossolini et al, 1991 (55,54)
Antigenically induced lesioning of the locus coeruleus promotes thymus involution and $CD4^+$ lymphocyte depletion of blood and suppresses the Arthus and delayed skin reactions	SRBA as antigen. Tuberculin as antigen	The sympathetic nervous system, by implication, contribute to thymic involution	Jankovic et al, 1994; Nikolic et al, 1993; Jovanova - (56,57)
Thymic sympathectomy enhances thymosin α_1 production	6-Hydroxydopamine (6OHD)	The sympathetic system suppresses the secretion of thymosin α_1 from epithelial cells	Hall et al, 1982 (58)

From published reports (see Table 4.1 for references) it can be deduced that

- Noradrenergic innervation of endothelial cells, epithelial cells, thymocytes, macrophages and mast cells have been established beyond doubt. Most of the noradrenaline found in the thymus appears to be of noradrenergic fibre origin, rather than being derived from the

circulating catecholamine pool.

- From ontogenic studies the adrenergic innervation would appear to be of little importance for prenatal thymic development as innervation is predominantly a postnatal development.
- The first thymic effects during development are probably that on vascular diameter and thus on blood flow.
- The first parenchymal innervation during development is seen in the cortical zone that generally contains the immature thymocytes. This may imply that the sympathetic system is of importance for the early development of thymocytes and is supported by the reported positive catecholamine influence on differentiation and receptor expression. The second parenchymal area to develop adrenoceptor functionality is the cortico-medullary junction, which would suggest a role for NA in thymocyte migration.
- From published data it is conceivable that α_1-adrenergic receptors predominate on vascular and capsular elements, which would support the suggestion of an adrenergic control of thymus perfusion and, by implication, in cell traffic.
- Adrenoreceptors on the thymocytes and other parenchymal elements are predominantly $ß_2$, which is common for most metabolic/secretory adrenergically induced functions in the body. A variety of factors such as the sex steroids seem to be able to bring about an up or a down regulation in adrenoreceptor density and in the stimulated c-AMP response. Too little is, however, known about the context, in terms of other factors of the thymic microenvironment in which these alterations occur, in order to come to any conclusion for the thymus *per se*.
- An increase in adrenoceptor density with a concomitant suppression of the stimulus responsiveness would appear to accompany the maturation of thymocytes. Whether this phenomenon reflects part of the maturation process, or whether it is merely a function of noradrenaline availability is not yet clear.
- The apparent positive effect of NA on thymocyte early development, differentiation and on receptor expression as well as the suppression of thymic hormonal activity in the absence of NA, may point toward a role for the sympathetic system in enhancing thymus-dependent immunity during the early stages.
- Despite thymic innervation being predominantly a postnatal development, the innervation is, in contrast to other lymphoid organs, maintained for a longer period than that of the spleen - with peak density found during thymic involution. This might merely

be a reflection of the shrinkage of the thymic mass, without a concomitant decrease in the number of adrenergic fibres. However indications, are that the sympathetic system might be involved in thymic involution as lesioning of the locus coeruleus promotes thymic involution.

- Integrating the implied stimulation on early development, the possibility that NA may be involved in eventual thymic involution, would suggest both a developmental and an inhibitory role for the sympathetic nervous system in the cellular immune system.
- It would further appear as if sympathetic stimulation may have an inhibitory effect on the thymic epithelial cell secretory function as thymosin α_1 increases after pharmacological sympathectomy.
- Thymic extract has in turn been shown to increase cerebral α_1-adrenoceptor density.
- The localisation of monoaminergic and peptidergic substances in the same fibres points towards the modulation of sympathetic activity by other neurotransmitters.
- Certain interactions such as the effect of thymic hormones on the maintenance of adrenergic responsiveness have been shown. A functional interdependency is also known to exist between adrenergic activities on the one hand, and steroid hormones, as well as a number of thymic humoral substances.

It is clear that a multitude of substances are involved in the immunology of the thymus and that it is virtually impossible to decipher the role of any individual factor. A further confounding factor in establishing the effect of the sympathetic system on thymic function is that very few of the workers tried to distinguish between acute and chronic noradrenergic influences. This is important as it is well known that acute and chronic stress-induced neuroendocrine alteration of the immune system may differ.

In conclusion it appears reasonable to assume that the CNA/SAM-axis affects thymic immune functions

- by regulating postnatal thymic perfusion and thus also cellular migration and maturation
- by being a factor in the control of the microenvironment of the thymus
- by being necessary for normal thymic developmental immunocompetence but
- by also being involved in the control of excessive immunological responses and in thymic involution

4.1.2 Effect of the primary lymphoid organs on the noradrenergic system.

It would appear that the primary lymphoid organs, and in particular the thymus, might have a positive effects on the nervous system. Very little is known about the effect on the CNA/SAM system *per se*. It has however been shown that thymic grafting can restore ß-adrenergic responsiveness and that thymic extracts can increase α_1-adrenoceptor density. This increase in density was however seen to be accompanied by a decrease in receptor-mediated responsiveness (55). Whether these two effects occur simultaneously, and whether it has any functional implication is not clear.

However, indications are that the thymus may be necessary for the maturation of the neuroendocrine system during early life and that it might perhaps also play a role in the neuroendocrine secretory functions of the adult brain. This is substantiated by the fact that neuroendocrine abnormalities are known to result from either the congenital absence of the thymus or from neonatal thymectomy. (59,60) A possible regulatory role on neuroendocrine function is further seen in the effect of thymus-derived immunoregulatory substances on neuroendocrine function (61). See Table 4.2.

Table 4.2: Influence of thymus-derived substances on the neurological system

THYMIC FACTOR	EFFECT ON NERVOUS SYSTEM
Thymosin $ß_4$	Stimulates hypothalamic-pituitary-gonadal axis in vitro
Thymosin α_1	Stimulates hypothalamic-pituitary-adrenal axis in vivo
Thymosin F_5	Stimulates hypothalamic-pituitary-adrenal axis in vivo
Lymphokines	Decrease hypothalamic noradrenaline
Lymphokines	Stimulate glial cells
Interleukin 1	Stimulates hypothalamic thermoregulatory centres
Interleukin 1	Stimulates slow-wave sleep
$C3_a$	Modulates feeding behaviour at level of hypothalamus
ACTH	(Neural and pituitary peptide also produced by lymphocytes)

ß-Endorphin	(Neural and pituitary peptide also produced by lymphocytes)
Interferon	Induces lethargy and depression

Adapted from Hall et al, 1985 (61). See references in 61.

The thymic effects on the nervous system would appear to decline with aging. This apparently results from the combined effects of the age-associated thymus involution and a desensitisation of the neuroendocrine tissues to thymus-derived immunotransmitter substances.

4.1.3 Summary on the bidirectional interaction between the CNA/SAM-axis and the primary lymphoid organs.

In conclusion it can be said that

- the neuroendocrine system would appear to be essential for the ontogenic development of the thymus
- the thymus is in turn necessary for the early development and maintenance of the neuroendocrine system
- a bidirectional influence exists between the thymus and the neuroendocrine system with regard to secretory and other cellular functions
- although the nervous system is essential for the development of thymus-dependent immunocompetence, it is also involved in restraining unwarranted cellular immunity and in thymic involution
- the adrenergic influence on thymic function should not be seen as a major independent effect but rather as one aspect of the neuroendocrine, immunotransmitter milieu that regulates thymus function.

The interaction between the primary lymphoid organs and the CNA/SAM-axis is summarised on the next page in Figure 4.2.

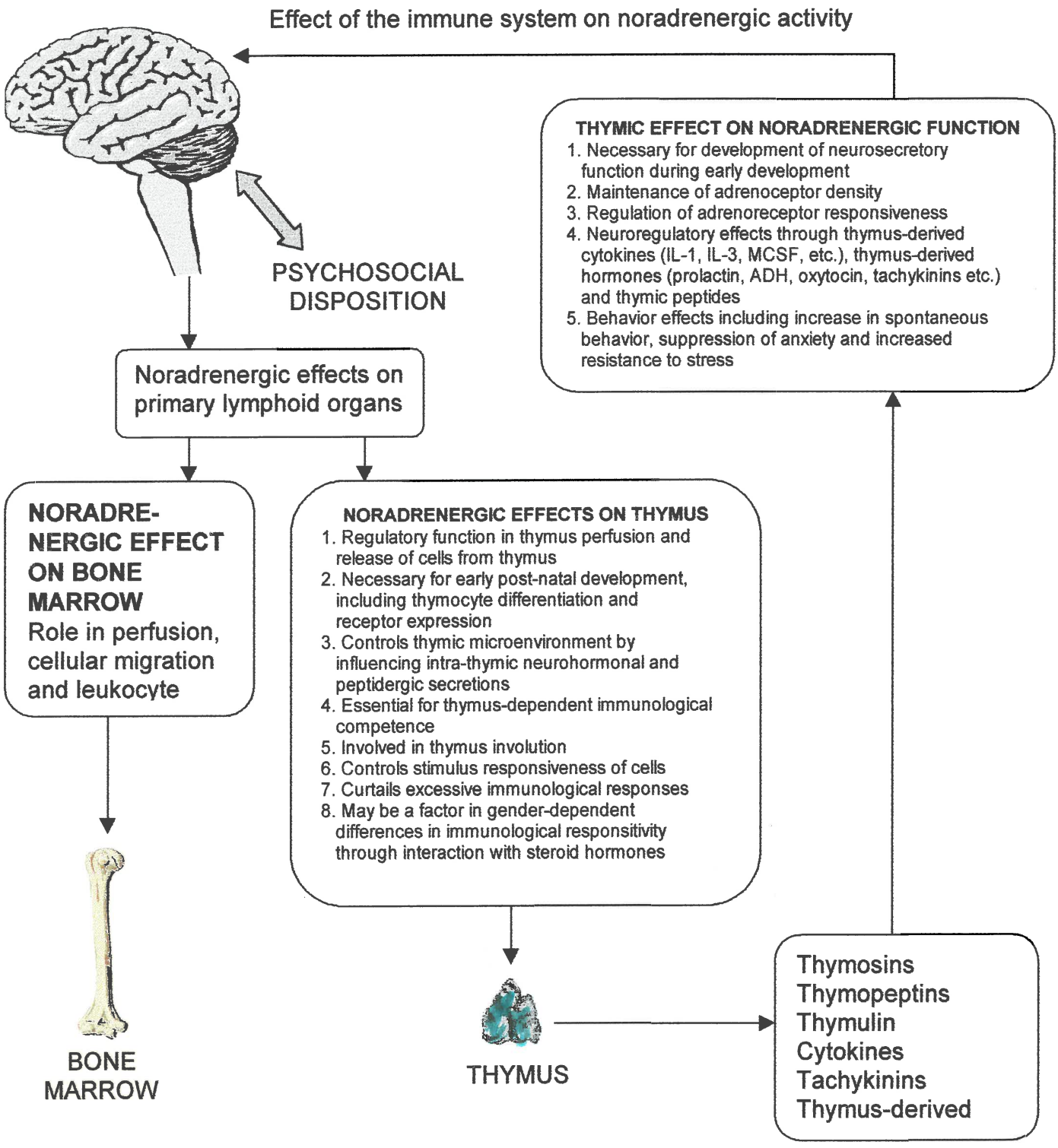


Figure 4.2: Bidirectional interaction between the primary lymphoid organs and the CNA/SAM-axis

4.2 Bi-directional interaction between the CNA/SAM-axis and the secondary lymphoid organs

4.2.1 Effect of the CNA/SAM-axis on the secondary lymphoid organs

A comprehensive discussion, including all the work done on the adrenergic influence on secondary lymphoid organ immunity is beyond the scope of this writing. The results of representative publications dealing with the innervation and some of the major findings on the influence of the noradrenergic system on secondary lymphoid organs are summarised in Table 4.3.

Table 4.3: Noradrenergic influence on secondary lymphoid organs

ORGAN	OBSERVATION	TECHNIQUE	FUNCTIONAL IMPLICATION	REFERENCES
SPLEEN	1.NA fibres along splenic artery, central artery and its branches, the peri-ateriolar lymphatic sheath (PALS), and in assoiation with capsular and trabecular systems and in splenic parenchyma (marginal sinus, the marginal zone, parafollicular zone)	Electron microscopy Fluorescence histochemistry Isolated perfused human spleen Double-lable immunocyto-chemistry	Early findings on vascular and capsular innervation point towards a role in smooth muscle contraction and thus resistance to blood flow	Ader et al, 1990; Felten et al, 1987; Felten et al, 1987; Felten and Felten 1992; Felten et al, 1992; Williams and Felten 1981; Ackerman et al, 1991. (64,65,66,67,17, 31,29)
	2.No innervation of B-cell follicles could be shown with fluorescence histochemistry. Single fibres into follicles could only be shown by double lable immunocytochemistry	Double lable immuno-cytochemistry Fluorescence histochemistry	Sympathetic innervation of follicles is minimal or absent	Felten et al, 1987 (65)
	3.Fibres in red pulp mainly in areas adjacent to trabecular and venous plexuses	Fluorescence histo-chemistry	Sympathetic effect predominantly On blood flow?	Felten et al, 1985 (66)
	4.Cell bodies of post ganglionic fibres to spleen situated either in the paravertebral ganglia or coeliac-superior mesentric ganglionic complex		Indicates innervation pathway	Bellinger et al, 1989 Nance and Burns, 1989 (38,68)
	5.TH^+ nerve fibres in pposition to $CD19^+$ T-cells, T-helper cells and T-cytotoxic cells of the PALS, the $CD19^+$ T-cells and $SIgM^+$B-cells of the para-follicular zone as well as the $ED3^+$ macrophages and IgM^+B-cells of the marginal Sinus	Double-lable immuno-cytochemistry	Direct contact exists between SAM axes and splenic cells – Evidence for neural immune interaction at splenic cellular level	Felten et al, 1987a Felten et al, 1987b Felten et al, 1992 (65,66,67)
	6.Close association between fibres and cellular elements of white pulp	Electron microscopy	Cryptocine arrangement	Galindo and Imaeda, 1962 (69)
	7.Direct close apposition between NA nerve terminals and lymphocytes and macrophages of the white pulp appositions are closer than smooth muscle synapses or neuro-effector junctions	Immunocytochemistry (TH^+ specific antibodies)	Imply direct influence for the sympathetic system on splenic lymphocytes and macrophages	Felten and Olschowka, 1987 Felten et al, 1987b (70,66)
	8.Innervation declines with age in parallel with a decline in the number of splenic lymphocytes and macrophages	Fluorescence histo-chemistry	In contrast to thymus where no decrease occur	Ackerman et al, 1991 (29)
	9.Destruction of NA fibre terminals all but completely clear the spleen of NA	Neurotoxin destruction or/and ganglionectomy HPLC	The majority of splenic NA is of NA fibre origin	Bellinger et al, 1989 Felten et al, 1987b Williams et al, 1981

			(38,66,34)
10.More common to find innervation in association with T-dependent than with B-dependent areas. Areas which contain mixed cells i.e. T-lymphocytes, B-lymphocytes, macrophages, etc. are largely innervated by noradrenergic/ NPY containing fibres	Histochemistry	More significant influence of NA on the cellular than humoral immunity	Felten et al 1987a+b (65,66)
11.Splenic diameter decreases with intravenous administration of α_1-adrenergic stimulants (dogs)	Adrenergic stimulants Sonomicrometry	Splenic contraction is mediated through α_1-adrenoceptor activity	Ojiri et al, 1993 (71)
12.The suppressive effect of morphine on conA-stimulated proliferation of splenic lymphocytes is mediated through macrophage derived nitric oxide	Pharmacological manipulation of lymphocyte functions	Splenic macrophages are innervated by adrenergic fibres but effects often indirect	Fecho et al, 1994 (72)
13.The majority of splenic adrenoceptors belong to class B_2 and are found in the capsule, marginal zone of red and white pulp with low densities in the white pulp	[125] cyanopindolol autoradiography	It is suggested that beta-adrenoceptors are present on mature splenic cells and not likely to be involved in homing mechanisms	Fernandez-Lopez et al, 1994 (73)
14.Increase in lymphocyte and granulocyte release from the spleen after NA and ISO injection. Blocked by both phentolamine and propanolol without a change in blood flow	Pharmacological manipulation	Release not a mere blood flow-induced phenomenon. Both α and ß-adrenoceptors involved	Ernström and Sandberg, 1973 Ernström and Soder, 1975 (74,75)
15.The SNS inhibits antigen processing/presentation and T-helper cell response	in vivo	Immune suppression by SNS	Heilig et al, 1993 (76)
16.Propanolol suppresses the conditioned prevention of adjuvant-induced arthritis	Pavlovian conditioning	The sympathetic suppressor effect on splenic proliferation is mediated through ß-receptors	Lysle et al, 1991 (77)
17.Propanalol blocks the conditioned suppressive effect on splenic mitogen responsiveness	Pavlovian conditioning	Conditioned immune alterations of splenic lymphocytes are mediated through ß-receptors	Lysle et al, 1991 (77)
18.The alpha adrenoceptor antagonist phentolamine blocks the cold stress augmentation of mitogen - induced splenic lymphocyte IgG and IgM production. Beta blockers enhance the effects of cold stres	Pharmacological intervention	Both alpha and beta effects on the immune response and the two may directly oppose each other	Carr et al, 1993 (78)
19.Pretreatment with a non-selective ß-adrenergic antagonist, a $ß_1$ antagonist as well as a $ß_2$ antagonist prevents the suppressive effect of morphine on mitogen induced proliferation of splenic cells	Pharmacological manipulation	ß-adrenoceptors are involved in the immune suppressive effect of morphine	Fecho et al, 1993 (79)
20.Suppressor T-cells have the highest density, cytotoxic T-cells and intermediate density and helper T-cells the lowest drenoceptor density. Splenic ß-cells (in mice) express twice the number of ß-adrenoceptors than T-cells	Ligand binding	1.May be a noradrenaline up or down regulation 2.ß-cells may be influenced by NA from adjacent areas	Kahn et al, 1986 Van Tits et al, 1990 Kobilka, 1992 Fuchs et al, 1988 (80,81,82,83)
21.Spleen cell adrenoceptor density decrease with immunisation	SRBC immunization	Lymphocyte activation changed (α) ß-adrenoceptor density	Fuchs et al, 1988 (83)
22.NA and ISO enhances LPS induced proliferation and differentiation of splenic lymphocytes	in vitro exposure	ß-effect (blocked by propanolol)	Kouassi et al, 1988 (84)

LYMPH NODES AND LYMPHOID TISSUE OF GIT	1.NA fibres enter lymphnodes at hilus, run along vasculature, distribute in medullary cords amongst mixed populations of lymphocytes and macrophages in subcapsular regions spares innervation of ß-lymphocyte follicles	Fluorescence histochemistry Double lable immunocyto-chemistry	Same general pattern as spleen	Ackerman et al, 1987 Felten et al, 1987b Felten et al, 1984 Felten et al, 1981 Felten et al, 1992 Giron et al, 1980 Madden and Felten, 1995 (85,66,86,87,88, 89)
	2.In lymph nodes NA fibres found within subcapsular zone, paracortical regions, cortical regions, medullary cords. No obvious innervation of ß-cell follicles	Fluorescence histo-chemistry Double-lable immunocyto-chemistry	Same general pattern as spleen	Felten and Felten, 1991 Felten et al, 1987a Giron et al, 1980 Madden and Felten, 1995 (77,65,88,89)
	3.In rodents NA fibres to cervical, mesentric and popliteal lymph nodes. Decline in number and activity as a function of age	Fluorescence histo-chemistry	Possibly a concomitant decrease of NA Innervation/function and cell-mediated immune function. Corresponds to spleen. Opposite from thymus	Bellinger et al, 1989 Madden and Felten, 1995 (38,89)
	4.Substances which raise intracellular C-GMP augment the release of lymphocytes	Administration of serotonin and substance P	Multiple influences on release of lymphocytes from lymph nodes	Moore, 1984 (90)
	5.Infusion of dbcAMP decreases lymphocyte release. Infusion of dbcGMP increases lymphocyte release	Chemical sympathectomy	The autonomic system should by implication thus be able to regulate lymphocyte release directly – not a blood flow phenomenon	Moore and Lachman, 1982 (91)
	6.Sympathectomy enhances the collection of lymphocytes in lymphnodes and decreases the migration of lymphocytes from lymphnodes	in vitro - isolated lymph-node perfusion	An inhibitory effect on circulating lymphocyte numbers	Madden and Livnat, 1991 (92)
	7.The primary antibody response in sympathectomized animals varies from unaltered, to enhanced to suppressed	6-hydroxydopamine	6-hydroxydopamine sympathectomy has wider neural effects and fibre regrowth may occur. Adrenal medullary catecholamines may effect intact receptors	Miles et al, 1981 Besedovsky et al, 1979 Hall et al, 1982 Madden and Livnat, 1991 (93,94,95,92)
GALT (Gut associated lymphoid tissue)	1.NA fibres of GIT lymphoid tissue distributed through T-dependent zones and in lamina propria. No evidence of ß-lymphocyte follicle innervation	Electron microscopy Fluorescence histo-chemistry, etc.	Corresponds to other secondary lymphoid tissue. Indicates a direct influence of sympathetic nervous system on lymphocyte trafficking, antigen processing and presentation as well as on T-cell function, B-cells maybe affected by sympathetically altered T-cell functions such as altered cytokine production	Felten and Felten, 1991 Felten et al, 1987 Giron et al, 1980 (17,65,88)

SNS = Sympathetic nervous system; NA = noradrenaline; GIT = gastro-intestinal; SRBC = sheep red blood cell; LPS = lipopolysaccharide

The following discussion is based on publications referred to in the table above and on a number of publications of which the references appear in the text.

In contrast to the thymus, i.e. to primary lymphoid tissue, noradrenergic innervation of the secondary lymphoid organs is present during the early developmental periods and declines with age. The noradrenergic innervation of the spleen appears to precede the development of the cellular elements, which would imply a role for the sympathetic nervous system in the developmental and maturational processes. An age-dependent decline in the adrenergic innervation would appear to parallel the decrease in the number of splenic lymphocytes and macrophages.

The distribution of noradrenergic innervation to secondary lymphoid organs implies a direct role for the sympathetic nervous system in mechanisms such as lymphocyte trafficking, antigen processing, antigen presentation and as a result, T-lymphocyte functional integrity. B-cell function would, if affected, be influenced, either indirectly by noradrenaline-induced changes in T-cell and macrophage activity or by cytokine production, or directly by noradrenaline, diffusing from fibres, not in direct contact with B-cells.

It is clear that the CNA/SAM-axis effect on the spleen and other secondary lymphoid organs depends on

- the adrenergic receptor type
- the concentration of noradrenaline
- the receptor density
- the presence of peptidergic innervation
- the presence of cytokines
- the cell-type involved in the immune response
- the antigenicity of the stimulus
- the time of adrenergic stimulation relative to the antigen stimulation
- the duration of the adrenergic stimulation (acute or chronic)
- the activation state of the immune cells at the time of noradrenergic stimulation.

The reader is referred to Table 4.3 and to a number of reviews for more details on the effects of the above-mentioned factors on the adrenergically –induced alterations in the secondary lymphoid organ immune response (62,35,63 29,8).

4.2.2 Summary of the bidirectional interaction between the CNA/SAM-axis and the secondary lymphoid organs.

From Table 4.3, and in considering from the number of factors that may be influential in determining splenic immune reactivity in response to adrenergic stimulation, it is evident that the sympathetic influence can't summarily be described as either inhibitory or stimulatory. Probably the best, yet vastly oversimplified, way to summarise the effect of the adrenergic influence on secondary lymphoid tissue would be to say that noradrenergic stimulation:

- may either enhance or inhibit the immune response - depending on the context
- augments the primary immune response
- enhances the activation or initiation of cell-mediated responses
- inhibits end-stage effector cell functions
- is essential for immunocompetence but suppresses immune function at high levels of noradrenaline
- would under basal conditions, appear to have a tonic inhibitory role which helps to curtail autoimmunity

Indications are that splenic immune responses may in turn influence the nervous system. This would be discussed in the next section as such effects are often not distinguishable form that of the circulating immunocompetent cells.

The interaction between the secondary lymphoid organs and the CNA/SAM-axis (noradrenergic activity) is summarised in Figure 4.3 (next page).

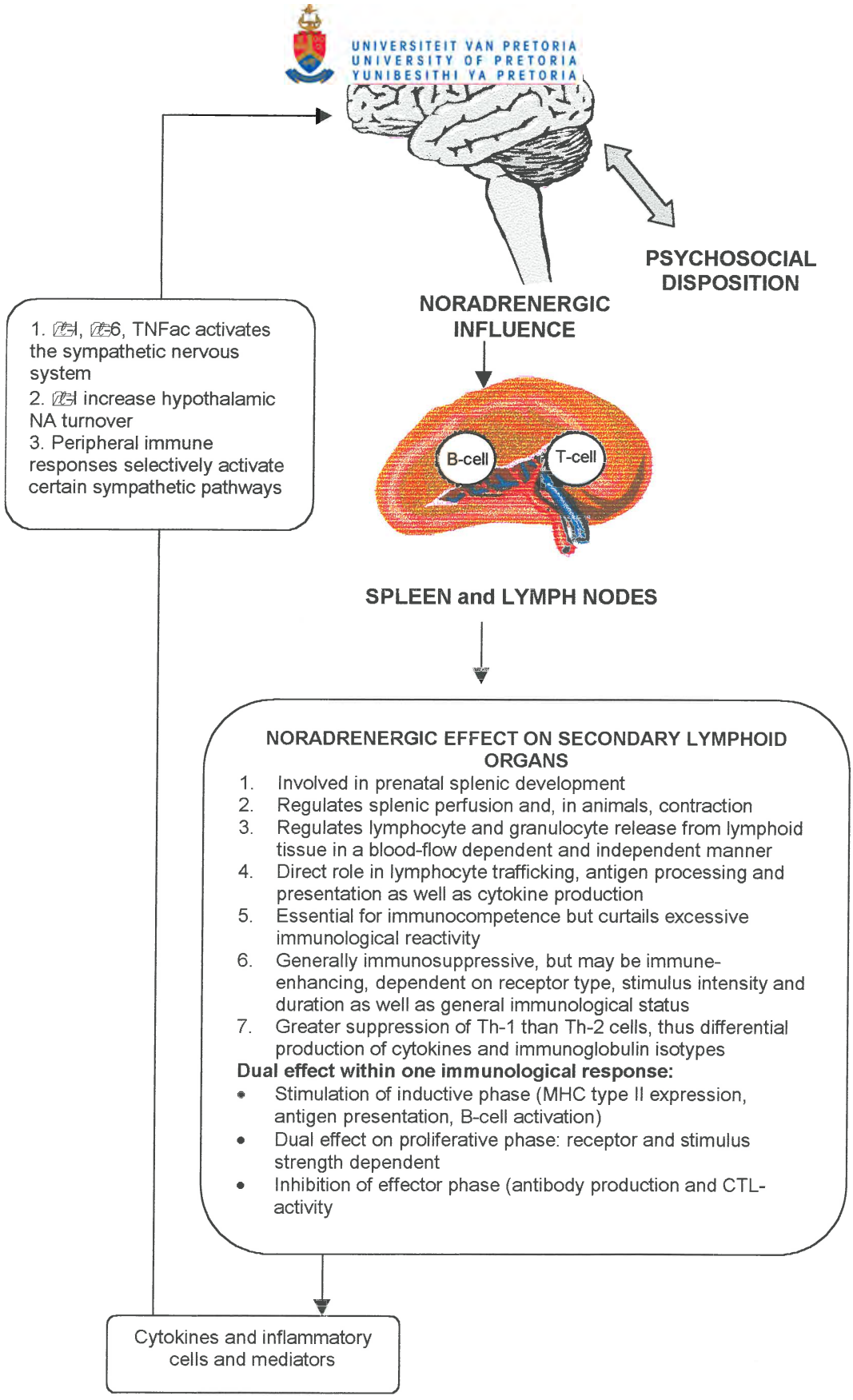


Figure 4.3: Bidirectional interaction between the secondary lymphoid organs and the CNA/SAM-axis

4.3. Bidirectional interaction between the CNA/SAM-axis, the circulating immunocompetent cells and *in vivo* immunity.

4.3.1 Effects of the CNA/SAM-axis on circulating immune cells and *in vivo* immunity.

Some of the major findings concerning the effects of sympathetic stimulation on immune cells and on *in vivo* immunological competency are referred to in Table 4.4. The following synoptic discussion is based largely on publications referred to in Table 4.4 and on references listed in Table 4.4. All references are therefore not duplicated in this discussion. The table does not include all available or only original publications as such a compilation would be beyond the scope of this writing. Because of the magnitude of the published work, references to review articles rather than original articles are sometimes provided.

Beta-adrenoceptors are found on T-and on ß-lymphocytes, macrophages, monocytes, neutrophils, basophils and on eosinophils. These receptors are upregulated in the presence of ß-blockers and down-regulated in the presence of ß-agonists, increased with cellular maturation and may increase or decrease with mitogen stimulation - depending on the signal transduction pathway [This was reviewed by Madden and Felden, 1995 (62)]. The response upon a noradrenergically induced increase in cAMP depends on the receptor density, the signal pathway, the duration of the stimulus, the time of stimulation relative to the immune stimulus, the summation of other influences and on previous immunisations (See Table 4.4 for references).

Table 4.4: The effect of sympathetic stimulation on immunological cells and on general *in vivo* immunocompetence

1. Early <u>in vitro</u> studies : a. ß-adrenoceptor stimulation (↑cAMP): Inhibition of lymphocyte proliferation, antibody secretion and production of pro-inflammatory substances b. α-adrenoceptor stimulation: Augmentation of lymphocyte proliferation, antibody secretion, production of pro-inflammatory substances	An oversimplification - complexity of interaction evidenced by following comments	Hadden et al, 1970 Melmon et al, 1974 Bourne et al, 1974 (98,99,100)
2. In general an inhibition of granulocyte function *(in vitro)*	*Inhibition of neutrophil phago-cytosis and lysozymal release *Inhibition of neutrophil respiratory burst *Decreased rate of superoxide production	Zurier et al, 1974 Nielson, 1987 Gibson-Berry et al, 1993 Yukawa et al, 1990 Rivkin et al, 1975

	*Shortened period of superoxide production (some contradiction) *Inhibition of antigen-induced histamine and SRS-A release from sensitized basophils and other cells (i.e. ↓ in IgE-mediated hypersensitivity) *A transient increase in circulating granulocytes with acute stimulation * ▼ NK cell cytotoxicity	Harvath et al, 1991 Lichtenstein and Margolis, 1968 Assem et al, 1969 Bourne et al, 1974 Ishizaka et al, 1971 Madden and Felton, 1995 (101,102,20,103, 104,105,106,107,99, 108,109,89)
3. Sympathetic stimulation can stimulate or suppress lymphocyte activity depending on the type of immunological stimulus (i.e. intracellular pathway) the duration of the stimulus and the sympathetic stimulation, the time of application of NA stimulation relative to time of stimulus (ß-cells/ß-adrenoceptor) (*in vitro*)	LPS + NA simultaneously : ↑ proliferation of spleen cells; LPS with later NA : no effect; NA ↑ proliferation after polyclonal ß-cell morigen; NA inhibits proliferation of anti IgM antibodies, differences between direct B-cell stimulation and antigen presenting cells induced stimulation	Li et al, 1990 Chartash et al, 1988 Kawakami et al, 1993 (110,111,112)
4. ß-adrenergic stimulation generally inhibits T-cell activity. Inhibition (if present) depends on ß-adrenoceptor density, duration of NA exposure and intracellular pathway (*in vitro*)	NA (and other factors which ↑cAMP)inhibits T-cell proliferation, Iℓ-2 production (↓anti-CD3-induced T-cell proliferation and enriched $CD4^+$, $CD8^+$, $CD45\ RO^+$ lymphocyte subpopulations)	Hadden et al, 1970 Kammer et al, 1988 Carlson et al, 1989 Bartik et al, 1993 (98,113,114,115)
5. Dual T-cell stimulation through ß-adrenergic and -cell receptors increases cAMP concen-tration and ▲ [CaMP] is generally associated with suppression of cell proliferation	* ▲ cAMP inhibits transmembrane signalling events which in turn prevent activated T-cells to transmit from the Go to the G1 of the cell cycle * ▲ cAMP suppresses the expression of proto-oncogenes c-myc and c-Ha-ras * ▲ cAMP in activated T-cells suppresses 1*l*-2 production	Reviewed by Roszman and Carlson, 1991 (96)
6. Lysis of cells by NK cells and Cytotoxic lymphocytes (CTL) are inhibited by ß-adrenoceptor stimulation in a dose dependent manner. Noradrenalin can influence macrophages and NK-cell activity either directly of through regulation of cytokine production *in vitro*	Lower doses (10^{-6}M) would appear to inhibited, and doses above 10^{-8}M may potentiate NK activity. CTL-induced target cell lysis is inhibited and exocytosis of granules suppressed by adrenergic stimulation	Katz et al. 1982 Hellstrand et al. 1985 Strom et al. 1973 (116,117,118)
7.a. ß-adrenoceptor activation generally inhibits stimulus- induced cytokine production (depending on timing of ß-adrenoceptor stimulation relative to immune stimulus) The reponsiveness of cells to cytokines is generally inhibited by adrenergic stimulation b. Synergistic action between	Inhibition of the production of TNF by monocytes and macrophages. IFN induced activation of macrophages is inhibited by NA. Inhibition further augmented by VIP (∴ ↑cAMP). ß-receptor stimulation +Iℓ-4 increase the expression of CD23 IgE receptors. Iℓ-2 induction of LAK cells increased by α-agonist	Severn et al, 1992 Spengler et al, 1994 Irimajiri et al, 1985 Koff and Dunegan, 1985 Beckner and Farrar, 1988 Paul-Eugene et al, 1993

adrenoceptor and cytokines may alter the response c. Isolated reports of cytokine stimula-tion by α-stimula-tion (*in vitro*)		(119,120,121,122,123,124)
8. Multicellular mechanistic Immune reponses indicate that ß-adrenergic stimulation might be essential for early events and might suppress the final events of antibody production. α-Receptors would appear to enchance the final immune reponse (*in vitro*)	NA added in beginning to cell cultures increases antibody response, NA added late in process inhibits immune response	Melmon et al, 1974 Sanders and Powell-Oliver, 1992 Ron and Sprent, 1987 (99,125,126)
9. Cytotoxic lymphocytes and antigen-induced proliferation need ß-adrenoceptor stimulation during early developmental stages. α-Stimulation may work in concert with ß-stimulation. Perhaps α and ß effects oppose each other with ß-stimulating early events and α stimulating later events with ß suppressing later stages and α earlier stages (*in vitro*)	Terbutalin and ISO at inital stages in mixed culture: ▲ CTL generation. Phentolamine: ↑lytic activity. Phenylephrine: ↓ antigen-specific proliferation of lymphoid cells	Hatfield et al, 1986 Heilig et al, 1993 Madden and Felten, 1995 (127,76,89)
10. *In vivo* experiments with chemical or surgical sympathectomy in adults indicate that sympathetic stimulation a. generally suppresses T-independent antibody responses and enhances T-dependent responses b. reduces cell mediated responses (delayed type hypersensitivity, Iℓ-2 production, CTL-activity) c. may increase of decrease cellular proliferation	a. Sympathectomy reduces antibody responses in adult rodents if 6-OHDA was used b. Neonatally sympathectomized adult aminals show enhanced antibody production - in an aged-dependent way c. Cell-mediated immune responses reduced after sympathectomy Opposite effects on T-dependentand T-independent antibody responses	Fuchs et al, 1988 Livnat et al, 1985 Hall et al, 1982 Kasahara et al, 1977 Madden and Felten, 1995 (26,128,95,129, 89)
11. Catecholamine infusion Showed that time of sympathetic stimulation relative to immune stimulus determines the immune effect. The acute effects include redistribution of immune cells and the chronic effect would indicate immune suppression (*in vivo*)	Early NA and continuous NA infusion inhibits T-cell proliferation and antibody response, but may lead to a transient increase in circulating immune cells (↑ release) - no change in blood flow	Felsner et al, 1992 Gader, 1974 Crary et al, 1983 Ernström and Sandberg, 1973 Ernström and Söder, 1975 McHale and Thornbury, 1990 (130,131,132,133,134,135)
12. The sympathetic system has a tonic inhibitory role in autoimmune disease : Observations in autoimmune and other pathologies, as well as in aging, indicate that a. the sympathetic system controls (↓) immunological reactions against "self-antigens" and in sodoing prevents auto-immune	Sympathectomy exacerbates experimental rheumatoid arthritis, hastens onset and augments inflammation and skeletal deterioration, of RA. A reduced NA activity associated with SLE, auto-immune haemolytic anaemia, and other auto-immune diseases	Levine et al, 1988 Breneman et al, 1993 Cunnick et al, 1990 Sonnenfeld et al, 1992 Dobbs et al, 1993 Madden and Felten, 1995

disease b. stress-induced enhancement of NA stimulation inhibits splenic T-cell proliferation, IFNδ production and increases vulnerability to herpes simplex and other infections agents (*in vivo*)		Rogers and Fozdar, 1996 (136,137,138,139,140,89,141)
13. Stress-induced decreases in $CD4^+$ cells, increases in NK-cell number and cytolytic activity are only significant in high sympathetic reactors to acute stress	The sympathetic system in the stress-induced modulation of the immune system is more pronounced in high sympathetic reactors to acute stress	Matthews et al, 1995 (142)
14. In auto-immune disease, sympathetic activity is reduced prior to onset of symptoms and chemical sympathectomy worsens the severity of the disease.	Evidence exists for an immune suppressor function	Madden et al, 1995 (35)
15. The immune modulatory effects of prolonged elevation of catecholamine levels differs from short term sympathetic stimulation and noradrenaline and adrenaline may have opposite immune modulating effects	Sympathetic effect depends on the duration of the stimulation and on the receptor type	Harris et al, 1995 (143)

It is, as was previously mentioned, clear that the effect of the sympathetic system on the immune system cannot summarily be considered as either inhibitory or stimulatory. The results of noradrenergic stimulation on the immune system has, for the major part, been analysed in terms of its stimulatory effect on intracellular cAMP levels. Within this context lie numerous factors that can complicate a simple deduction as to the effect of the sympathetic system on immunity. An example of this is the fact that cAMP has been reported to be essential for cellular maturation and proliferation (92) but that raised cAMP levels have also been said to suppress the expression of a number of proto-oncogenes. However, the expression of proto-oncogenes such as c-myc and c-Ha-ras are known to be important for the development of the proliferative potential of lymphocytes (96). Another confounding factor in drawing a parallel between *in vivo* sympathetic stimulation and the immune effect is the multitude of substances, other than noradrenaline, which are capable of modifying intracellular cAMP activity, some of them co-transmitters of the adrenergic system. A discussion on the control of intracellular cAMP activity is in itself a very wide subject that can easily be considered a separate independent field of research. It can, however, surely be seen as yet another connection between, or entrance for the cellular biologist into the field of psychoneuroimmunology, and by implication, into the field of psychology. A third group of confounding factors in

reading the sympathetic effect from the results of *in vivo* sympathetic stimulation is adrenoceptor distribution, expression and reactivity, but even more so the type of adrenoceptors present. Direct opposing effects have been ascribed to ß and α-receptors respectively and a variety of, especially ß-adrenoceptor subtypes, is presently being investigated.

It is therefore evident that the effect of sympathetic stimulation on *in vivo* immunoreactivity could never be interpreted as an irrevocable effect as it is intrinsically dependent on factors such as the physiological environment, the chronological order of immune vs. neurotransmitter stimulus, and the duration of the stimulus. In the light of our present knowledge and insight it is perhaps only possible to summarise the general effects in broad terms.

As such it is possible to say that it has by now unequivocally been established that the sympathetic system can, depending on the internal environmental context, exert, either a stimulatory or inhibitory influence on the immune system. It is further feasible that both stimulating and inhibiting influences may be exerted within the same immunological response. Such a potentially dual modulatory role for the adrenergic system has earlier been postulated by Madden and Livnat (92) describing

- a stimulating role during the inductive phase of the immune reponse
- either a stimulatory or inhibitory role, depending on the strength of the noradrenergic impact, during the proliferative phase
- an inhibitory role during the effector phase

In view of the complexity of predicting the effect of the noradrenergic influence on specific immune responses it would perhaps be more apt to try and define the influence on total *in vivo* immunocompetence. In such an assessment of immunological functionality one should consider the immune responsiveness to noradrenergic stimuli as well as the role in self-tolerance. A role for the adrenergic system has been described for both. The adrenergic effect on immunological responsiveness would appear to be of a dual nature, i.e., it could be immunostimulatory or immunorestraining.
An immunorestraining function for the sympathetic system is evident in (see table 4.4, as

well as reviews 35, 29 and 92 for references)

- it's reported role in prevention of autoimmune diseases
- the increased vulnerability to herpes simplex and other microbial agents during periods of excessive, stress induced sympathetic activity and
- in the enhancement of certain immune responses in the presence of sympathectomy and adrenoceptor blockers

An immunostimulating role from the noradrenergic system has also been confirmed established. The necessity of a functionally intact adrenergic system for immunocompetence is highlighted in an overview by Ackerman et al, (29) which deals with the ontogeny and senescence of the noradrenergic system's influence on immunological affecters. It is perhaps best illustrated by the similarity between the effects of ageing and that of sympathectomy. Similarities between the age-associated decline in immunocompetence and the effects of sympathetic denervation on the immune responsiveness can be seen in Table 4.5.

Table 4.5: A comparison between the effects of aging and the effects of chemical sympathectomy on the immune system.

IMMUNE RESPONSE	AGING	RESULT OF SYMPATHEC-TOMY
T-Cell responses		
Delayed-type hypersensitivity	▼	▼
Cytotoxic T-lymphocyte activity	▼	▼
con A-induced proliferation	▼	▼
Interleukin-2 production	▼	▼
Interleukin –2 receptors	▼	–
Polyclonal B-cell responses		
Lipopolysaccharide induced proliferation	▲▼	▲▼
Immunoglobulin secretion in reponse to poly-clonal B-cell stimulation	▲	▲
Antibody reponse		
Primary T-dependent antigen	▼	▼
Secondary T-dependent antigen	▲▼	▼
Primary T-independent antigen	▲▼	▲
Tumoricidal activity		
NK-cell activity	▲▼	▲
Resistance to tumor challenge	▼	▲

(Adapted from Ackerman et al, 1991 (29)) ; ▲=increased; ▼=decreased; ▲▼= increased or decreased.

More evidence in support of a role for the CNA/SAM-axis in immunocompetence was seen in the earlier subdivisions that dealt with the primary and secondary lymphoid organs, in the references in Tables 4.1,4.3 and 4.4, and in a multitude of other publications, not referred to in this writing.

It is further known that the psychological disposition of the individual plays a markedly dominant role in the immunoreactivity of the individual. This emotional influence is especially important in conditions of stress where both the two major stress axis, i.e. the HPA-axis and the CNA/SAM-axis, are stimulated. The degree to which an individual or animal feels in control of a situation would appear to be a major determinant in the outcome of this neurological influence on immunocompetence. Evidence points towards a role for the noradrenergic system in this respect (97). This is however dealt with in more detail in the chapter on the psychoimmunological interaction and in the final chapter.

In summary it can, with regard to the effect of the CNA/SAM-axis on circulating immune cells and total *in vivo* immunity, be said that

- a role for the sympathetic system in the control of the *in vivo* immune system has been shown beyond any doubt
- the magnitude on the adrenergic system on total immunity, relative to that of other influences such as other hormones and neuroactive agents, is still speculative
- the sympathetic system is necessary for immunological competence, especially during the developmental stages, but can also curb unwarranted immunological reactivity
- sympathetic activity may within the same immune response, stimulate the process (during the inductive phase) as well as suppress it (during the effector phase)
- it is feasible to accept that the outcome of high noradrenergic activity on the immune system depends on the perception of the individual. This psychological influence would, however, be deferred to a later chapter dealing primarily with this aspect.

4.3.2 Effects of circulating immune cells and substances on the CNA/SAM-axis.

The effect of the immune system on the nervous system can be assessed either through

ascertaining the alterations in the central noradrenergic system (CNA) function and structure, or by observation of the effects on peripheral adrenergic functions (SAM-axis). Direct immunological effects include (89).

- increased sympathetic firing rates in the adrenal medulla and spleen upon Iℓ-1 infusion
- increased firing rates in the ventro-medial hypothalamus, as well changes in adrenergic neurotransmitter concentrations and neuronal activity in diverse areas of the hypothalamus and brainstem upon either cytokine administration or immune stimulation
- a wide spectrum of neuroendocrine hormones which are secreted by immunological competent cells and which can either act as autocrine or paracrine regulatory hormones or can feed back to the central nervous system - especially the hypothalamus - to inhibit nervous system secretory activity. This might in turn affect central sympathetic activity
- the effects of immunologically derived cytokines that, over and above their many other central nervous effects, can modulate central noradrenergic functioning (144).

The exact cerebral targets are not always known, but peripherally derived cytokines have been implicated in a variety of psychological effects and even in some psychiatric disturbances. It was shown that such cytokines may be involved in changes in eating, sleeping and exploratory behaviour, as well as in socialisation and other behavioural functions and that they may be a factor in chronic fatigue, sickness behaviour and mood disturbances (145, 146). At present it would appear that the affects of the immune system on the central nervous system are mediated predominantly through immunologically derived cytokines and other inflammatory mediators. Various ways had been suggested by which these cytokines may reach their neural targets within the blood brain barrier (145). Cytokines are said to be transported across the blood brain barrier by cytokine-specific transport mechanisms or through areas with a high permeability for cytokines. Cytokines have further been shown to mediate their cerebral effects, either by binding to receptors on peripheral nerves, or by influencing the intracerebral prostaglandin production. There are also indications that the cytokine-producing leukocytes themselves may gain entry into the central nervous system to produce their cytokines *in situ*. Other substances said to be involved in the transduction of immunological occurrences into cerebral events include various immune modulators, as well as leukocyte-derived peptides and steroids. At least one of the

mechanisms mentioned has been shown to be involved in the immunological effect on the central noradrenergic system, i.e., the prostaglandin-dependent mechanism. In transmitting information about peripheral immunological event to the central nervous system, the immune system acts as yet another sensory system. The immune system has, in fact, in the past been likened to a sixth sense organ (147).

The effect of immunologically derived cytokines on the brain and on behaviour is the subject of Chapter 6. It is therefore necessary to summarise the influence of the sympathetic nervous system on cytokine production. Probably the most important point to be addressed is the differential effect of the catecholamines on the secretion of pro-inflammatory and anti-inflammatory cytokines. Stimulation of the β_2–adrenoceptor–cAMP-protein kinase pathway stimulates the production of anti-inflammatory cytokines such as interleukin-10 (IL-10), transforming growth factor-β (TGFβ), interleukin-4 (IL-4), interleukin-13 (IL-13) and suppresses the release of pro-inflammatory cytokines such as interferon-gamma (INFγ), interleukin-2 (IL-2) and tumour necrosis factor -alpha (TNFα). Stress-induced noradrenaline activity can therefore cause a suppression of T helper type 1 (Th1) responses and cellular immunity while stimulating T helper type 2 (Th2) responses and humoral immunity (148).

This is a very important aspect for anyone wanting to understand the effect of stress on conditions such as allergies, autoimmune diseases, chronic inflammatory conditions and probably the connection between stress-related mental disturbances and immune disturbances. However, it requires a cutting-edge knowledge of immunology and is therefore beyond the aim of this thesis. Some of the essential detail would be discussed in chapter 6 where the influence of the immune system on behaviour is dealt with.

4.4 Summary of the neuroimmunological interaction in terms of the CNA/SAM-axis.

The immune system has for long been considered an autonomous system with considerable self-regulatory capabilities. The same applies to the SAM-axis as one of the two major divisions of the autonomic nervous system. It is, however, becoming increasingly clear that the immune and sympathetic systems can be affected by other factors and that a bidirectional influence exist between them. Indications are that the bidirectional influence between the immune system and the CNA/SAM-axis can either be stimulatory or inhibitory, depending on the ontogenic stage, the

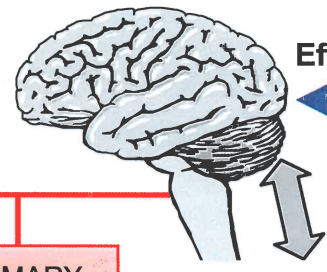
phase of the immunological reaction, the potency and duration of the stimulation as well as the magnitude of other neural and humoral influences. A sustained stimulatory bidirectional interaction would, in effect, represent a positive reverberating feedback loop between the two systems. This would appear to be the case during the early ontogenic period where sound immunological development seems to be dependent on normal functional development of the noradrenergic system, and *vice versa*. This positive functional interdependence probably exists for life - as can be seen in the effect of the immune system on receptor density and other factors, and in the positive effect of the sympathetic system during the early phases of immunological responses. However, it is evident that negative feedback between the two systems also exists, especially form the neural to the immunological system. This appears to be especially true during the effector phases of immune responses and with regard to the curtailing of unwarranted immunological activity. The CNA/SAM-axis would, in fact, appear to be a major restraining factor against the development of autoimmune disorders and in controlling certain inflammatory conditions. It would further appear that excessive noradrenergic activity, as seen during severe negative stress, could predispose to infections and tumour growth.

Recent indications of differential modulatory effects of stress-induced noradrenalin secretion on cytokine release offer extremely promising therapeutic possibilities for the treatment of stress-related disorders.

Perhaps the interactions between the two systems can best be summarised by saying that the immune system should indeed be seen as one more target of the central nervous system, and that the immune system can in turn act as an additional sensory organ informing the central nervous system about immunological related events and as such can serve as neurological, and by implication, as behavioural, response modifier.

The content of this chapter is presented on the next page, as Figure 4.4, as a heuristic diagram of the bidirectional interaction. As a small-scale version (Figure 4.1), it was also shown at the beginning of the chapter in an attempt to facilitate the reading of the chapter. It is given here in normal size as a summary of the work presented and because it is considerably easier to read.

NORADRENERGIC ACTIVITY and IMMUNITY



PHYCHOSOCIAL DISPOSITION

Effects of the immune system on the noradrenergic activity

THYMIC EFFECT ON NORADRENERGIC FUNCTION AND NORADRENERGIC CONTROL CENTRES

1. Necessary for development of neuro-secretory function during early development
2. Maintenance of adrenoceptor density
3. Regulation of adrenoreceptor responsiveness
4. Neuroregulatory effects through thymus-derived cytokines (IL-1, IL-3, MCSF, etc.), thymus-derived hormones (prolactin, ADH, oxytocin, tachykinins etc.) and thymic peptides
5. Behaviour effects include increase in spontaneous behaviour, suppression of anxiety and increased resistance to stress

NORADRENERGIC EFFECTS ON THYMUS

1. Regulatory function in thymus perfusion and release of cells from thymus
2. Necessary for early post-natal development, including thymocyte differentiation and receptor expression
3. Controls thymic micro-environment by influencing intra-thymic neurohormonal and peptidergic secretion
4. Essential for thymus-dependent immunological competence
5. Involved in thymus involution
6. Controls stimulus responsiveness of cells
7. Controls excessive immunological responses
8. May be a factor in gender-dependent differences in immunological responsitivity through interaction with steroid hormones

Effects on immune system

IN VIVO IMMUNO - REACTIVITY

SECONDARY LYMPH ORGANS

PRIMARY LYMPH ORGANS

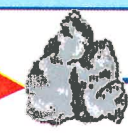
NORADRENERGIC EFFECT ON SECONDARY LYMPHOID ORGANS (SPLEEN)

1. Involved in prenatal splenic development
2. Regulates splenic perfusion
3. Regulates lymphocyte and granulocyte release from lymphoid tissue in a blood-flow dependent and independent manner
4. Direct role in lymphocyte trafficking, antigen processing and presentation as well as cytokines production
5. Essential for immunocompetence but curtails excessive immunological reactivity
6. Generally immunosuppressive, but may be immune-enhancing, dependent on receptor type, stimulus intensity and duration as well as general immunological status
7. Dual effect within same immunological reaction with stimulation in the inductive phase and inhibition in the effector phase
8. B_2-adrenoceptor-cAMP-protein kinase activity inhibits pro-inflammatory pathway and stimulates anti-inflammatory pathway through differential effects on TH1 and TH2 cells. Can shift immune response from cellular to humoral

NORADRENERGIC EFFECT ON BONE MARROW

Role in perfusion, cellular migration and leukocyte release

BONE MARROW

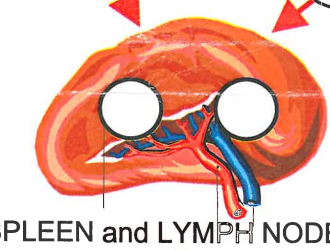


THYMUS

- Thymosins
- Thymopeptins
- Thymulin
- Cytokines
- Tachykinins
- Neurohypophysial hormones

B-cells

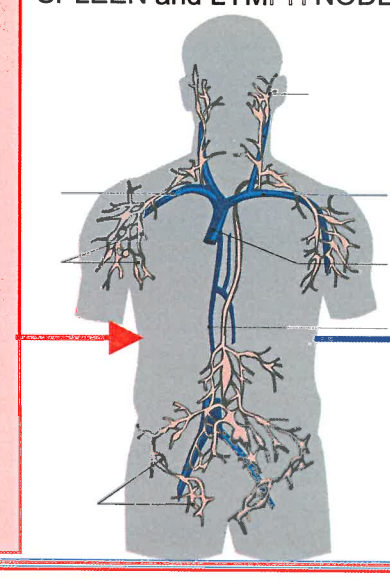
T-cells



SPLEEN and LYMPH NODES

NORADRENERGIC EFFECT ON IN VIVO IMMUNOREACTIVITY

1. Beta-adrenoceptors are found on lymphocytes, monocytes granulocytes and macrophage
2. Alpha-adrenoceptors are found on some immune cells and on vasculature (important in cell traffic and release)
3. Most phagocyte functions appear to be suppressed by NA
4. Essential for T-cell response (cytotoxic T-cell activity, Con A-induced proliferation, IL -2 production, IL -2 receptor expression, T-cell dependent antibody response) but control excessive reactivity
5. Tonic inhibition of tumoricidal activity (NK-cell activity etc) and T-independent antibody responses (polyclonal B-cell responses)
6. Inhibition of macrophage antigen presenting activity
7. Immunological effects of NA stimulation are dependent on receptor type and density, intensity and duration of stimulation as well as on stage of immunological reaction and immunology status
8. Effects on immune responses influence cytokine production
9. Helps to localize inflammatory response
10. Protects body from the tissue damage inflicted by overproduction of systemic proinflammatory cytokines
11. Stress-induced adrenergic stimulation may expose the body to infectious complications and autoimmune diseases and tumour growth
12. Hypoactivity may predispose to fibromyalgia/chronic fatigue syndrome



EFFECTS OF THE IMMUNE SYSTEM ON NEUROLOGICAL FUNCTION.

1. Sensory function
2. Affects neuronal firing rate
3. Affects rate of noradrenaline secretion and stimulates adrenoceptor expression
4. Regulatory feedback through immunocompetent cell-derived cytokines, neuro-endocrine and peptidergic substances
5. Possible antibody – induced cerebral effect
6. Stimulation of the central stress response with a basal tonic inhibitory effect on stress-related behaviour

SUMMARY OF NEUROIMMUNOLOGICAL INTERACTION EFFECTS OF NORADRENERGEC ACTIVITY ON IMMUNITY

1. Necessary for immunodevelopment and immunocompetence
2. Major factor in immunorestraint
3. Essential for self-tolerance (basal tonic inhibitory effect helps to curtail auto-immune reactivity)
4. Opposite effects with acute (enhancement) and chronic (suppression) hyperstimulation
5. Variations in noradrenergic activity implicated in tumourgenesis, chronic inflammatory disorders, stress-induced Immuno-incompetence and allergies
6. Implicated as a factor in the immune alterations obtained through conditioning and in immune alterations with drug abuse

EFFECTS OF THE IMMUNE SYSTEM ON NORADRENERGIC ACTIVITY

1. Necessary for neurosecretory development and maintenance of adrenoceptor expression and functional integrity
2. Acts as sensory system to alert CNS about peripheral infectious and immunological occurences
3. Immunologically-derived cytokines give rise to the central stress response through induction of stress hormone secretion
4. (HPA-axis and CNA/SAM-axis) and inhibition of anti-stress hormones (GH, LH, FSH etc)
5. Immunologically-derived cytokines implicated in behavioural effects such as sickness behaviour, mood changes, sleep, eat and locomotor disturbances, anxiety, as well as exploratory, coping and related behavioural phenomena
6. Excessive immunological inflammatory activity may predispose to psychological disorders
7. Cytokine therapy can have neurotoxic effects partially mediated via central NA system

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Figure 4.4: A schematic representation of the bidirectional interaction between the CNA/SAM-axis and the immune system.

Legend to Figure 4.4

Figure 4.4: A schematic representation of the bidirectional interaction between the CNA/SAM-axis and the immune system

[On the left hand side of the diagram the effects of the CNA/SAM-axis on primary lymphoid organ (thymus and bone marrow) immunity, secondary lymphoid organ (spleen and lymph nodes) immunity, and on *in vivo* immunological reactivity and competence are shown. The right hand side represents the effects of the immune system on the functional and developmental aspects of the CNA/SAM-axis. At the bottom of the page the overall effects are summarised.]

This chapter presented the neuroimmunological interaction between the CNA/SAM-axis and the immune system. In combination with the previous chapter, i.e., Chapter 3, it describes psychoneuroimmunology in terms of the CNA/SAM-axis. The next chapter will show the psychoneuroimmunological interaction in terms of the CRH/HPA-axis.

References

1. Dardenne M, Savino W. Prolactin-mediated cellular interaction in the thymus. Ann NY Acad Sci 1994;741:101-107.

2. Dardenne M and Savino W. Neuroendocrine circuits controlling the physiology of the thymic epithelium. Ann NY Acad Sci 1992; 650:85-90.

3. Savino W, Dardenne M, Papiernik M, Bach JF. Thymic hormone containing cells. Characterization and localization of serum thymic factor in young mouse thymus studied by monoclonal antibodies. J Exp Med 1982;156:628-634.

4. Goldstern AL, Low TLK, Thurman GB, Zatz MM, Hall NR, Chen J, Hu SK, Naylor PB, McClure JE. Current status of thymosin and other hormones of the thymus gland. Recent Prog Horm Res 1981;37:369.

5. Spangelo BL, Hall NR, Goldstein AL. Biology and chemistry of thymosin peptides. Modulators of immunity and neuroendocrine circuits. Ann NY Acad Sci,1987;496:196-204.

6. Le PT, Tuck DT, Dinarello CA, Haynes BF, Singer KH. Thymic epithelial cells produce interleukin 1. J Immunol 1988;138:2520-2525.

7. Le PT, Lazorich S, Whichard LP, Yang YC, Clark SC, Haynes BF, Singer KH. Human thymic epithelial cells produce Iℓ-6, granulocyte-monocyte CSF and leukemia inhibitory factor. J Immunol 1990;145:3310-3315.

8. Bellinger DL, Lorton D, Felten SY, Felten DL. Innervation of lymphoid organs and implications in development, ageing and autoimmunity. Int J Immunopharmacol 1992;14:329-344.

9. Savino W, Villa-Verde DM, Lannes Vieira J. Extracellular matrix proteins in intrathymic T cell migration and differentiation. Immunol Today 1993;14:158-161.

10. Mocchegiani E, Santarelli L, Fabris N. Thymic endocrine function in neuroendocrine human disease. Ann NY Acad Sci 1991;741:115-123.

11. Geenen V, Cormann-Goffin N, Vandermissen E, Martens H, Benhida A, Martial J, Franchimont P. Cryptocrine signaling in the thymus network. Ann NY Acad Sci 1994;741:85-99.

12. Dardenne M, Savino W. Neuroendocrine control of thymic epithelium. Modulation of thymic endocrine function, cytokeratin expression and cell proliferation by hormones and neuropeptides. Prog Neuro Endocrin Immunol 1990;3:18-25.

13. Felten SY, Felten DL. Innervation of lymphoid tissue. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology. San Diego, CA Acad vol II, 1991, pp27-68.

14. Bellinger DL, Lorton D, Romano T, Olschowka JA, Felten SY, Felten DL. Neuropeptide innervation of lymphoid organs. Ann NY Acad.Sci 1990;594:17-33.

15. Calvo W. The innervation of the bone marrow in laboratory animals. Am J Anat 1968;123:315-328.

16. Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S. Noradrenergic and peptidergic innervation of lymphoid tissue. J Immunol 1985;135:755s-765s.

17. Felten SY, Felten DL. Innervation of lymphoid tissue. In: JE Blalock (ed). Chemical Immunology: Neuroimmunoendocrinology. Basel, Karger, 1991, pp25-48.

18. Calvo W, Haas RJ. Die histogenese des Knochemarks der Ratte. Z Zellforsch 1969;95:377-395.

19. Miller ML , McCuskey RS. Innervation of bone marrow in the rabbit. Scand. J Haematol 1973;10:17-23.

20. Gibson-Berry KL, Richardson C, Felten SY, Felten DL. Immunocytochemical and neurochemical analyses of sympathetic nerves in rat bone marrow. Soc Neurosci Abstr 1993;19:944.

21. Maestroni GJM, Conti A, Pedrinis E. Effect of adrenergic agents on hematopoiesis after syngeneic bone marrow transplantation in mice. Blood 1992; 80:1178-1182.

22. Takase B, Nomura S. Studies on the innervation of the bone marrow. J Comp Neurol 1957;108:421-443.

23. De Pace DM, Webber RH. Electrostimulation and morphologic study of the nerves to the bone marrow of the albino rat. Act Anat 1975;93:1-18,

24. Tran MA, Tran DL, Lafontan M, Montastruc P. Adrenergic neurohumoral influences on FFA release from bone marrow adipose tissue. J Pharmacol 1985; 16(2):171-179.

25. Rossolini G, Viticchi C, Basso A, Zaia A, Piantanelli L. Thymus-induced recovery of age-related decrease of brain cortex alpha- and beta-adrenoceptors. Int J Neurosci 1991;59(1-3):143-150.

26. Fuchs BA, Campbell KS, Munson AE. Norepinephrine and serotonin content of the murine spleen: Its relationship to lymphocyte ß-adrenergic receptor density and the humoral immune reponse *in vivo* and *in vitro*. Cell Immunol 1988;117: 339-351.

27. Bach MA. Differences in cyclic AMP changes after stimulation by prostaglandins and isoproterenol in lymphocyte subpopulations. J Clin Invest 1975;55:1074-1081.

28. Bulloch K, Pomerantz W. Autonomic nervous system innervation of thymic related lymphoid tissue in wild-type and nude mice. J Comp Neurol 1984;228: 57-68.

29. Ackerman KD, Bellinger DL, Felten SY and Felten DL. Ontogeny and senescence of noradrenergic innervation of the rodent thymus and spleen. In: Robert Ader, David Felten, Nicolas Cohen (eds). Psychoneuroimmunology (2nd ed) , San Diego, Academic Press Inc. 1991.

30. Singh U. Sympathetic innervation of fetal mouse thymus. Eur J Immunol 1984; 14:757-759.

31. Williams JM, Felten DL. Sympathetic innervation of murine thymus and spleen : a comparative histofluorescence study. Anat Rec 1981;199:531-542.

32. Tollefson L, Bulloch K. Dual-label retrograde transport: CNS innervation of the mouse thymus distinct from other mediastinum viscera. J Neurosci 1990;25:20-28.

33. Bellinger DL, Felten SY, Felten DL. Maintenance of noradrenergic sympathetic innervation in the involuted thymus of the aged Fischer 344 rat. Brain Behav Immun 1988;2:133-150.

34. Williams JM, Peterson RG, Shea PA, Schmedtje JF, Bauer DC, Felten DL. Sympathetic innervation of murine thymus and spleen: evidence for a functional link between the nervous and immune systems. Brain Res Bull 1981;6:83-94.

35. Madden KS, Sanders VM, Felten DL. Catecholamine influences and sympathetic neural modulation of immune responsiveness. Ann Rev Pharmacol Toxicol 1995;35:417-448.

36. Bulloch K, Cullen MR, Schwarts RH, Longo DL. Development of innervation within syngeneic thymus tissue transplanted under the kidney capsule of the nude mouse. A light and ultrastructural microscope study. J Neurosci Res 1987;18: 16-27.

37. Singh U. Effect of catecholamines on lymphopoiesis in fetal mouse thymic explants. J Anat 1979;129:279-292.

38. Bellinger DL, Felten SY, Lorton D, Felten DL. Origin of noradrenergic innervation of the spleen in rats. Brain Behav Immun 1989;3:291-311.

39. Singh U, Owen JJT. Studies on the maturation of thymus stem cells. The effects of catecholamines, histamine, and peptide hormones on the expression of T alloantigens. Eur J Immunol 1976; 6:59-62.

40. Singh U, Millson S, Smith PA, Owen JJT. Identification of ß-adrenoceptors during thymocyte ontogeny in mice. Eur J Immunol 197;9:31-35.

41. Marchetti B, Morale MC, Pelletier G. The thymus gland as a major target for the central nervous system and the neuroendocrine system: Neuroendocrine modulation of thymic beta$_2$-adrenergic receptor distribution as revealed by in vitro autoradiography. Mol Cell Neurosci 1990;1:10-19.

42. Marchetti B, Morale MC, Pelletier G. Sympathetic nervous system control of thymus gland maturation: autoradiographic characterization and localization of the beta$_2$-adrenergic receptor in the rat thymus gland and presence of a sexual dimorphism during ontogenic development. Progr Neuroendocrine Immunol 1990;3:103-115.

43. Marchetti B, Labrie F. Hormonal regulation of beta-adrenergic receptors in the rat mammary gland during the oestrous cycle and lactation: role of sex steroids and prolactin. Endocrinology 1990;125:575-581.

44. MacManus JP, Whitheld JF, Youdale I. Stimulation by epinephrine of adenyl cyclase activity, cyclic AMP formation. DNA synthesis and cell proliferation in populations of rat thymic lymphocytes. J Cell Phys 1971;77:103-116.

45. Scheid MP, Hoffman MK, Komuro K, Hammerling U, Abbott J, Boyse EA, Cohen GH, Hooper JA, Schulof RS, Goldstein AL. Differentiation of T cells induced by preparations from thymus and by nonthymic agents. J Experimental Med 1973;138:1027-1032.

46. Scheid MP, Goldstein G, Hammerling U, Boyse EA. Lymphocyte differentiation from precursor cells in vitro. Ann NY Acad Sci 1975;249:531-540.

47. Singh U, Owen JJT. Studies on the effect of various agents on the maturation of thymus stem cells. Eur J Immunol 1975;5:286-288.

48. Wan W, Vriend CY, Wetmore L, Gartner JG, Greenberg AH, Nance DM. The effects of stress on splenic immune function are mediated by splenic nerve. Brain Res Bull 1993;30:101-105.

49. Kendall MD, Al-Shawaf AA. Innervation of the rat thymus gland. Brain Behav Immun 1991;5:9-28.

50. Singh U. Effect of sympathectomy on the maturation of fetal thymocytes grown within the anterior eye chambers in mice. Adv in Exp Med and Biol 1985;186:349-356.

51. Singh U. Lymphopoiesis in the nude fetal mouse thymus following sympathectomy. Cell Immunol 1985;93:222-228.

52. Morale MC, Gallo F, Batticane N, Marchetti B. The immune response evokes up- and down-modulation of adrenergic receptor messenger RNA concentration in the male rat thymus. Mol Endocrinol 1992;6:1513-1524.

53. Kubera M, Skowron-Cendrzak A, Mazur-Kolecka B, Bubak-Satora M, Basta-Kaim A, Laskowska-Bozek H, Ryzewski J. Stress-induced changes in muscarinic and beta-adrenergic binding sites on rat thymocytes and lymphocytes. J Neuroimmol 1992 ;37(3):229-235.

54. Rossolini G, Viticchi C, Basso A, Zaia A, Piantanelli L. Thymus-induced recovery of age-related decrease of brain cortex alpha- and beta-adrenoceptors. Int J Neurosci 1991;59(1-3):143-150.

55. Basso A, Piantanelli L, Rossolini G, Amici D, Gianfranceschi GL. Differential influence of a thymic extract on alpha- and beta-adrenoceptors of mouse brain cortex. Ann NY Acad Sci 1994;741:124-128.

56. Jankovic BD. Neuroimmunomodulation : From phenomenology to molecular evidence. Ann NY Acad Sci. Vol 741, 1994.

57. Nikolic V, Javanova-Nesic K, Jankovic BD. Locus cerculeus and immunity. Int J Neurosci 1993;68:238-287.

58. Hall NR, McClure JE, Hu S-K, Tare NS, Seals CM, Goldstein, AL. Effects of 6-hydroxydopamine upon primary and secondary thymus dependent immune responses. Immunopharmacology 1982;5:39-48.

59. Pierpaoli E, Sorkin E. Alteration of adrenal cortex and thyroid in mice with congenital absence of the thymus. Nature 1972;238:282-285.

60. Goya RG, Sosa YE, Brown OA, Dardenne M. *In Vitro* studies on the thymus pituitary axis in young and old rats. Ann NY Acad Sci 1994;741:108-114.

61. Hall NR, McGills JP, Spangelo BL, Goldtein AL. Evidence that thymosins and other biological response modifiers can function as neuroactive immunotransmitters. J Immun 1985;135:806s-811s.

62. Madden KS, Sanders VM, Felten DL. Catecholamine influences and sympathetic neural modulation of immune responsiveness. Ann Rev Pharmacol 1995;35:417-448.

63. Besedovsky HO, Del Rey A. Physiological implications of the immune-neuroendocrine network. In: Ader, Felten and Cohen (Eds) Psychoneuroimmunology, (2nd ed.). Academic Press San Diego, 1991, pp589-608.

64. Ader R, Felten DL, Cohen N. Interactions between the brain and the immune system. Ann Rev Pharmacol Toxicol 1990;30:561-602.

65. Felten DL, Felten SY, Bellinger DL, Carlson SL, Ackerman KD *et al.* Noradrenergic sympathetic neural interactions with the immune system: structure and function. Immunol Rev 1987;100:225 –260.

66. Felten DL, Ackerman KD, Wiegand SJ, Felten SY. Noradrenergic sympathetic innervation of the spleen. I. Nerve fibres associate with lymphocytes and macrophages in specific compartments of the splenic white pulp. J Neurosci Res 1987;18:28-36.

67. Felten DL, Felten SY, Bellinger DL, Lorton D. Noradrenegic and peptidergic innervation of secondary lymphoid organs: role in experimental rheumatoid arthritis. Eur.J Clin Invest 1992;22:37-41.

68. Nance DM, Burns J. Innervation of the spleen in the rat : evidence for absence of afferent innervation. Brain Behav Immun 1989;3:218-230.

69. Galindo B, Imaeda T. Electron microscopic study of the white pulp of the mouse spleen. Anat Rec 1962;143:399-415.

70. Felten SY, Olschowka JA. Noradrenergic sympathetic innervation of the spleen: II. Tyrosine hydroxylase (TH)-positive nerve terminals from synaptic-like contracts on lymphocytes in the splenic white pulp. J Neurosci Res 1987;18:37-48.

71. Ojiri Y, Noguchi K, Chibana T, Sakanashi M. Effects of adrenergic stimulants on the splenic diameter. Haemoglobin content and haematocrit in anaesthetized dogs: determination of the adrenoceptor subtype responsible for changes in the splenic diameter. Acta Physiol Scand 1993;149:31-39.

72. Fecho K, Maslonek KA, Coussons-Read ME, Dykstra LA, Lysle DT. Macrophage-derived nitric oxide is involved in the depressed in the concacalin. A responsiveness of splenic lymphocytes from rats administered morphine *in vivo*. J Immunol 1994;152(12):5845.

73. Fernandez-Lopez A, Revilla V, Candelas MA, Aller MI, Soria C and Pazos A. Identification of ß-adrenoceptors in rat lymph nodes and spleen: an autoradiographic study. Eur Pharmacol 1994; 262:283-286.

74. Ernström U, Sandberg G. Effects of alpha- and beta-receptor stimulation on the release of lymphocytes and granulocytes from the spleen. Scand J Haematol 1973;11:275-286.

75. Ernström U, Soder O. Influence of adrenaline on the dissemination of antibody-producing cells from the spleen. Clin Exp Immunol 1975;21:131-140.

76. Heilig M, Irwin M, Grewal I, Sercarz E. Sympathetic regulation of T-helper cell function. Brain Behav Immunol 1993;7:154-163.

77. Lysle DT, Cinnuck JE, Maslonek KA. Pharmacological manipulation of immune alterations induced by an adverse conditioned stimulus: evidence for a beta-adrenergic receptor-mediated Pavlovian conditioned process. Behav Neurosci 1991;105(3):443-449.

78. Carr JA, Ortiz KA, Paxton LL, Saland LC, Savage DD. Alterations in spleen norepinephrine and lymphocyte [3H] dihydroalprenolol binding site number in genetically epilepsy prone rats. Brain Behav Immun 1993;7(2):113-120.

79. Fecho K, Dykstra LA, Lysle DT. Evidence for beta-adrenergic involvement in the immunomedulatory effect of morphine. J Pharmacol Exp Ther 1993;265(3):1079-1087.

80. Khan MM, Sansoni P, Silverman ED, Engleman EG. Beta-adrenergic receptors on human suppressor, helper, and cytolytic lymphocytes. Biochem Pharmacol 1986;35:1137-1142.

81. Van Tits LJH, Michel MC, Grosse-Wilde H, Happel M, Eigler FW. Catecholamines increase lymphocyte $ß_2$-adrenergic receptors via a $ß_2$-adrenergic, spleen-dependent process. Am J Physiol 1990;258:E191-E202.

82. Kobilka B. Adrenergic receptors as models for G protein-coupled receptors. Ann Rev Neurosci 1992;15:87-114.

83. Fuchs BA, Albright JW, Albright JF. ß-adrenergic receptors on murine lymphocytes : Density varies with cell maturity and lymphocyte subtype and is decresed after antigen administration. Cell Immunol 1988;114:231-245.

84. Kauassi E, Li YS, Boukhris W, Millet I, Revillard JP. Opposite effects of the catecholamines dopamine and norepinephrine on murine polyclonal B-cell activation. Immunopharmacol 1988;16:125-137.

85. Ackerman KD, Felten SY, Bellinger DL, Felten DL. Noradrenergic sympathetic innervation of the spleen III. Development of innervation in the rat spleen. J Neurosci Res 1987;18:49-54.

86. Felten DL, Livnat S, Felten SY, Carlson SL, Bellinger DL, Yeh P. Sympathetic innervation of lymph nodes in mice. Brain Res Bull 1984;13:693-699.

87. Felten DL, Overhage M, Felten SY, Schmedtje JF. Noradrenergic sympathetic innervation of lymphoid tissue in the rabbit appendix: further evidence for a link between the nervous and immune systems. Brain Res Bull 1981;7:595-612.

88. Giron LT, Crutcher KA, Davis JN. Lymph nodes - a possible site for sympathetic neuronal regulation of immune responses. Ann Neurol 1980;8:520-522.

89. Madden KS, Felten DL. Experimental basis for neural-immune interactions. Physiol Rev 1995;75:77-101.

90. Moore TC. Modification of lymphocyte traffic at vasoactive neurotransmitter substances. Immunology 1984;52:511-518.

91. Moore TC, Lachman PJ. Cyclic AMP reduces and cyclic GMP increases the traffic of lymphocytes through peripheral lymph nodes of sheep *in vivo*. Immunology 1982;47:423-428.

92. Madden KS, Livnat S. Catecholamine action and immunologic reactivity. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology. San Diego C : Academic press, 1991, pp283-310.

93. Miles K, Quintans J, Chelmicka-Schorr E, Arnason BGW. The sympathetic nervous system modulates antibody response to thymus-independent antigens. J Neuroimmunol 1981;1:101-105.

94. Besedovsky HO, Del Rey AE, Sorkin E, Da Prada DA, Keller HH. Immunoregulation mediated by the sympathetic nervous system. Cell Immunol 1979;48:346-355.

95. Hall NR, McClure JE, Hu SK, Tare NS, Seals CM, Goldstein AL. Effects of 6-Immunopharmacology 1982;5:39-48.

96. Roszman TL, Carlson SL. Neurotransmitters and molecular signalling in the immune response. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology, San Diego CA : Acad . Vol II, 1991, pp311-335.

97. Rotenberg VS, Sirota P, Elizur A. Psychoneuroimmunology : searching for the main deteriorating psychobehavioral factor. Genetic, Social and General Psychology Monographs 1996;122(3):329-346.

98. Hadden JW, Hadden EM, Middelton E Jr. Lymphocyte blast transformation. I. Demonstration of adrenergic receptors in human peripheral lymphocytes. Cell Immunol 1970;1:583-595.

99. Melmon KL, Bourne HR, Wienstein Y, Shearer GM, Kram J, Bauminger M. Hemolytic plaque formation by leukocytes *in vivo*. Control by vasoactive hormones. J Clin Invest 1974;53:13-21.

100. Bourne HR, Lichtenstein LM, Melmon K, Henney CS, Wienstein Y, Shearer GM. Modulation of inflammation and immunity by cyclic AMP. Science 1974;184: 19-28.

101. Zurier RB, Weissman G, Hoffstein S, Kammerman S, Tai HH. Mechanisms of lysosomal enzyme release from human leukocytes: II. Effects of cAMP and cGMP, autonomic agonists, and agents which affect microtubule function. J Clin Invest 1974;53:297-309.

102. Nielson CP. ß-adrenergic modulation of the polymorphonuclear leukocyte respiratory burst is dependent upon the mechanisms of cell activation. J Immunol 1987;139:2392-2397.

103. Yukawa T, Ukena D, Kroegel C, Chanez P, Dent G, et al. Beta 2-adrenergic receptors on eosinophils. Am. Rev Respir Dis 1990;141:1446-1452.

104. Rivkin I, Rosenblatt J, Becker EL. The role of cyclic AMP in the chemotactic responsiveness and spontaneous motility of rabbit peritoneal neutrophils. The inhibition of neutrophil movement and the elevation of cyclic AMP levels by catecholamines, prostaglandins, theophyline, and cholera toxin. J Immunol 1975; 115:1126-1134.

105. Harvath L, Robbins JD, Russel AA, Seamon KB. cAMP and human neutrophil chemotaxis. Elevation of cAMP differentially affects chemotactic responsiveness. J Immunol 1991;146:224-232.

106. Lichtenstein LM, Margolis S. Histamine release in vitro : inhibition by catecholamines and methylxanthenes. Science 1968;16:902-903.

107. Assem ESK, Schild HO. Inhibition by sympathomimetic amines of histamine release induced by antigen in passively sensitized human lung. Nature 1969;224 : 1028-1029.

108. Kagitani F, Kimura A, Sato A, Suzuki A. The role of the spinal cord as a reflex center for the somatically induced reflex responses of splenic sympathetic and natural killer cell activity in anesthetized rats. Neuro Sci Lett 1996;217(2-3): 109-112.

109. Ishizaka T, Ishizaka K, Orange RP, Austen KF. Pharmacologic inhibition of the antigen-induced release of histamine and slow reacting substance of anaphylaxis (SRS-A) from monkey lung tissues mediated by human IgE. Immunol 1971;106 :1267-1273.

110. Li YS, Kouassi E, Revillard J-P. Differential regulation of mouse B-cell activation by ß-adrenoceptor stimulation depending on type of mitogens. Immunol 1990; 69:367-372.

111. Chartash EK, Imai A, Gershengorn MC, Crow MK, Friedman SM. Direct human T-helper cell-mediated B cell activation is not mediated by inositol lipid hydrolysis. J Immunol 1988;140:1974-1981.

112. Kawakami K, Parker DC. Antigen and helper T lymphocytes activate B lymphocytes by distinct signaling pathways. Eur J Immunol 1993;23:77-84.

113. Kammer GM, Boehm CA, Rudolph SA, Schultz LA. Mobility of the human T lymphocyte surface molecules CD3, CD4 and CD8: regulation by a cAMP-dependent pathway. Proc Natl Acad Sci USA 1988; 85:792-796.

114. Carlson SL, Brooks WH, Roszman TL. Neurotransmitter-lymphocyte interactions : dual receptor modulation of lymphocyte proliferation and cAMP production. J Neuroimmunol 1989; 24:155-162.

115. Bartik MM, Brooks WH, Roszman TL. Modulation of T cell proliferation by stimulation of the ß-adrenergic receptor : lack of correlation between inhibition of T cell proliferation and cAMP accumulation. Cell Immunol 1993;148:408-421.

116. Katz P, Zaytoun AM, Fauci AS. Mechanisms of human cell-mediated cytotoxicity. I. Modulation of natural killer cell activity by cyclic nucleotides. J Immunol 1982;129:287-296.

117. Hellstrand K, Hermodsson S, Strannegard O. Evidence for a ß-adrenoceptor-mediated regulation of human natural killer cells. J Immunol 1985;134(6):4095-4099.

118. Strom TB, Carpenter CB, Garovoy MR, Austen KF, Merril JP, Kaliner M. The modulating influence of cyclic nucleotides upon lymphocyte-mediated cytotoxicity. J Exp Med 1973;138:381-393.

119. Severn A, Rapson NT, Hunter CA, Liew FY. Regulation of tumor necrosis factor production by adrenaline and ß-adreneric agonists. J Immunol 1992;148:3441-3445.

120. Spengler RN, Chensue SW, Giacherio DA, Blenk N, Kunkel SL. Endogenous norepinephrine regulates tumor necrosis factor α- production from macrophages in vitro. J Immunol 1994;152:3024-3031.

121. Irimajiri N, Bloom ET, Makinodan T. Suppression of murine natural killer cell activity by adherent cells from aging mice. Mech Ageing Dev 1985;31:155-162.

122. Koff WC, Dunegan MA. Modulation of macrophage-mediated tumoricidal activity by neuropeptides and neurohormones. J Immunol 1985;135:350-354.

123. Beckner SK, Farrar WL. Potentiation of lymphokine-activated killer cell differentiation and lymphocyte proliferation by stimulation of protein kinase C or inhibition of adenylate cyclase. J Immunol 1988;140:208-214.

124. Paul-Eugene N, Dugas B, Gordon J, Kolb JP, Cairns JA, *et al.* $ß_2$-adrenoceptor stimulation augments the IL-4-induced CD23 expression and release and the expression of differentiation markers (CD14, CD18) by the human monocytic cell line, U 937. Clin Exp Allergy 1993;23:317-325.

125. Sanders VM, Powell-Oliver FE. $ß_2$-adrenoceptor stimulation increases the number of antigen-specific precursor B lymphocytes that differentiate into IgM-secreting cells without affecting burst size. J Immunol 1992;148:1822-1828.

126. Ron Y, Sprent J. T cell priming *in vivo* : a major role for B cells in presenting antigen to T cells in lymph nodes. J Immunol 1987;138:2848-2856.

127. Hatfield SM, Petersen BH, DiMicco JA. ß-adrenoceptor modulation of the generation of murine cytotoxic T lymphocytes *in vitro*. J Pharmacol Exp Ther 1986;239:460-466.

128. Livnat S, Felten SY, Carlson SL, Bellinger DL, Felten DL. Involvement of peripheral and central catecholamine systems in neural-immune interactions. J Neuroimmunol 1985;10:5-30.

129. Kasahara K, Tanaka S, Ito R, Hamashima Y. Suppression of the primary immune response by chemical sympathectomy. Res Commun Chem Pathol Pharmacol 1977;16:687-693.

130. Felsner P, Hofer D, Rinner I, Mange H, Gruber M, *et al*. Continuous *in vivo* treatment with catecholamines suppresses *in vitro* reactivity of rat peripheral blood T-lymphocytes via mediated mechanisms. J Neuroimmunol 1992;37:47-57.

131. Gader AMA. The effects of beta-adrenergic blockage on the response of leucocyte counts to intravenous epinephrine in man. Scand J Haematol 1974;13: 11-16.

132. Crary B, Hauser SL, Borysenko M, Kutz I, Hoban C, Ault KA, Weiner HL, Benson H. Epinephrine-induced changes in the distribution of lymphocyte subsets in peripheral blood of humans. J Immunol 1983;131:1178-1181.

133. Ernström U, Sandberg G. Effects of alpha- and beta-receptor stimulation on the release of lymphocytes and granulocytes form the spleen. Scand J Haematol 1973; 11:275-286.

134. Ernström U, Söder O. Influence of adrenaline on the dissemination of antibody-producing cells from the spleen. Clin Exp Immunol 1975;21:131-140.

135. McHale NG, Thornbury KD. Sympathetic stimulation causes increased output of lymphocytes from the popliteal node in anaesthetized sheep. Exp Physiol 1990; 75:847-850.

136. Levine JD, Coderre TJ, Helms C, Basbaum AI. $ß_2$-adrenergic mechanisms in experimental arthritis. Proc Natl Acad Sci USA 1988;85:4553-4556.

137. Brenemann SM, Moynihan JA, Grota LJ, Felten DL, Felten SY. Splenic norepinephrine is decreased in MRL-Ipr/Ipr mice. Brain Behav Immunol 1993;7: 135-143.

138. Cunnick JE, Lysle DT, Kucinski BJ, Rabin BS. Evidence that shock-induced immune suppression is mediated by adrenal hormones and peripheral ß-adrenergic receptors. Pharmacol Biochem Behav 1990;36:645-651.

139. Sonnefeld G, Cunnick JE, Armfield AV, Wood PG, Rabin BS. Stress-induced alterations in interferon production and class II histocompatibility antigen expression. Brain Behav Immunol 1992;6:170-178.

140. Dobbs CM, Vasquez M, Glaser R, Sheridan JF. Mechanisms of stress-induced modulation of viral pathogenesis and immunity. J Neuroimmunol 1993;48:151-160.

141. Rogers MP, Fozdar M. Psychoneuroimmunology of autoimmune disorders. Advances in Neuroimmunology 1996;6(2):169-177.

142. Matthews KA, Gaggiula AR, McAllister CG et al. Sympathetic reactivity to acute stress and immune responses in women. Psychosom Med 1995;57:564-571.

143. Harris TJ, Waltman TJ, Carter SM, Maisel AS. Effect of prolonged catecholamine infusion on immunoregulatory function: implications in congestive heart failure. J Am Col Cardiol 1995;26(1):102-109.

144. Terao A, Oikawa M, Saito M. Cytokine-induced changes in hypothalamic noradrenaline turnover: involvement of corticotrophin-releasing hormone and prostaglandins. Brain. Res 1993;2:8-15.

145. Watkins A. Mind-body pathways. In: Mind-body Medicine. Alan Watkins (Ed) Churchill Livingstone, NY, 1997.

146. Psychoimmunology. CNS-Immune interactions. Alan J Husband (Ed). CRC Press, Inc., Florida 1993.

147. Blalock JE. The immune system: Our sixth sense. Immunologist 1984;2:8-15.

148. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve – An integrative interface between two super systems: the brain and the immune system. Pharmacol Rev 2000;52:595-638.

CHAPTER 5

THE PSYCHONEUROIMMUNOLOGICAL INTERACTION IN TERMS OF THE CRH/HPA-AXIS.

The Central Role of CRH in the Psychoneuroimmunological Interaction of the Two Main Stress Axes

The previous two chapters demonstrated the psychoneuroimmunological interaction in terms of the first of the two major stress axes, i.e., the central noradrenergic/peripheral sympathoadrenomedullary system (CNA/SAM-axis). This chapter deals with psychoneuroimmunology in terms of the other major stress axis, i.e., the central corticotropin-releasing hormone/peripheral hypothalamo-pituitary-adrenocortical axis (CRH/HPA-axis). In the CNA/SAM-axis the neurotransmitter noradrenaline plays a pivotal role in both the central and peripheral effects, while cortisol is generally seen as the main effector hormone of the CRH/HPA-axis, both for immunological and behavioural functions. In depth scrutiny of the subject lead to the conclusion that the last assumption is a misconception. This chapter will show that a) CRH is the dominant neurohormonal factor of the CRH/HPA-axis and that, in this role, controls not only the neurological-behavioural functions, but also the immunological reactivity and status, and b) that it not only regulates CRH/HPA-axis activity, but is also in control of the CNA/SAM-axis. The aim of the first section of this chapter is to demonstrate the distribution of CRH neurons in the central nervous system, as well as the central role of CRH in the integration and regulation of autonomic nervous system activity, neuroendocrine function and in behaviour. The second section will deal with the central role of the CRH/HPA-axis in immunological homeostasis, i.e., the neuroimmunological role of the CRH/HPA-axis. The third section demonstrates the central role of CRH in psychoneuroimmunology in terms of both major stress axes.

Introduction

Chapter 2 provided evidence for an interaction between the psychological disposition and the immune system, i.e., for a psychoimmunological link. It focussed on providing prove that enough evidence exists for the interaction to be considered a normal phenomenon of all behavioural processes and psychological abnormalities, and that behaviour can in almost all circumstances become a biological response modifier and *vice versa*. The underlying mechanisms that link the psychological and immunological events were at that stage largely ignored. The next step was to show the main stress axes, i.e., the CNA/SAM-axis and the CRH/HPA-axis, as underlying psychoneuroimmunological mediators. The third and fourth chapters demonstrated that in terms of the CNA/SAM-axis, i.e., the third chapter dealt with the psychoneurological and the fourth chapter with the neuroimmunological interactions in terms of the CNA/SAM-axis. The current chapter concentrates on psychoneuroimmunology in terms of the CRH/HPA-axis. It demonstrates that corticotropin-releasing hormone (CRH), plays a central role in the integration of autonomic function, somatic motor function, neuroendocrine activity and behavioural functions, as well as in the neuroendocrine control of immunity.

The essence of psychoneuroimmunology in terms of the CRH/HPA-axis can be condensed into four large diagrams (Figures 5.1, 5.2, 5.3 and 5.4). These diagrams are presented right at the beginning of the chapter, followed by descriptive supporting evidence. A fifth key diagram (Figure 5.15) is found right at the end of the chapter and presents psychoneuroimmunology in terms of the two main stress axes. Other figures are included for explanatory purposes.

The contents of this chapter is thus summarized in Figures 5.1 to 5.4 and Figure 5.15. These figures are:

Figure 5.1: The psychoneurological interaction in terms of the CRH/ HPA-axis.
The central role of CRH in the control of the neurohormonal and behavioural stress response.

Figure 5.2: The neuroimmunological interaction in terms of the CRH/ HPA-axis. The central role of CRH in the neurohormonal control of immunity.

Figure 5.3: The effects of acute and chronic increases in glucocorticoids.

Figure 5.4: Outline of the central role of corticotropin-releasing hormone in psychoneuroimmunology in terms of the CRH/HPA-axis.

Figure 5.15: Psychoneuroimmunology in terms of the two main stress axes. The central role of corticotropin-releasing hormone.

In the paragraphs, following upon the figures, more detailed explanatory discussions will be provided. These explanatory discussions are subdivided into:

Section 5.1: The psychoneurological interaction in terms of the CRH/ HPA-axis. The central nervous system CRH system and the central role of CRH in the stress response.

In Section 5.1 the distribution of the CRH neurons throughout the CNS is discussed. It is demonstrated that the central, as well as the peripheral, stress response, including the CNA/SAM-axis, are under CRH control. The section explains and expands on Figure 5.1.

Section 5.2: The neuroimmunological interaction in terms of the CRH/ HPA-axis: The central role of CRH in the neurohormonal control of immunity

In this section it is shown that CRH is ultimately in control of the total immunological effects of the CRH/HPA-axis, as well as the immunological effects of other hormones of the stress response. The immunological effects of the hormones influenced by CRH will briefly be reviewed. This section explains and expands on Figure 5.2 and Figure 5.3.

Section 5.3: Psychoneuroimmunology in terms of the two main stress axes. The central role of corticotropin-releasing hormone.

This section combines work from the previous 2 sections, as well as from Chapter 3 and Chapter 4 in order to show CRH as the central element in psychoneuroimmunology in terms of the two main stress axes. It is summarized in Figure 5.15.

In the explanatory discussion of sections 1 and 2 some of the main figures are subdivided in order to facilitate the understanding of the chapter as a whole.

Figures 5.1 to 5.4, followed by their respective legends, are presented on the next eight pages.

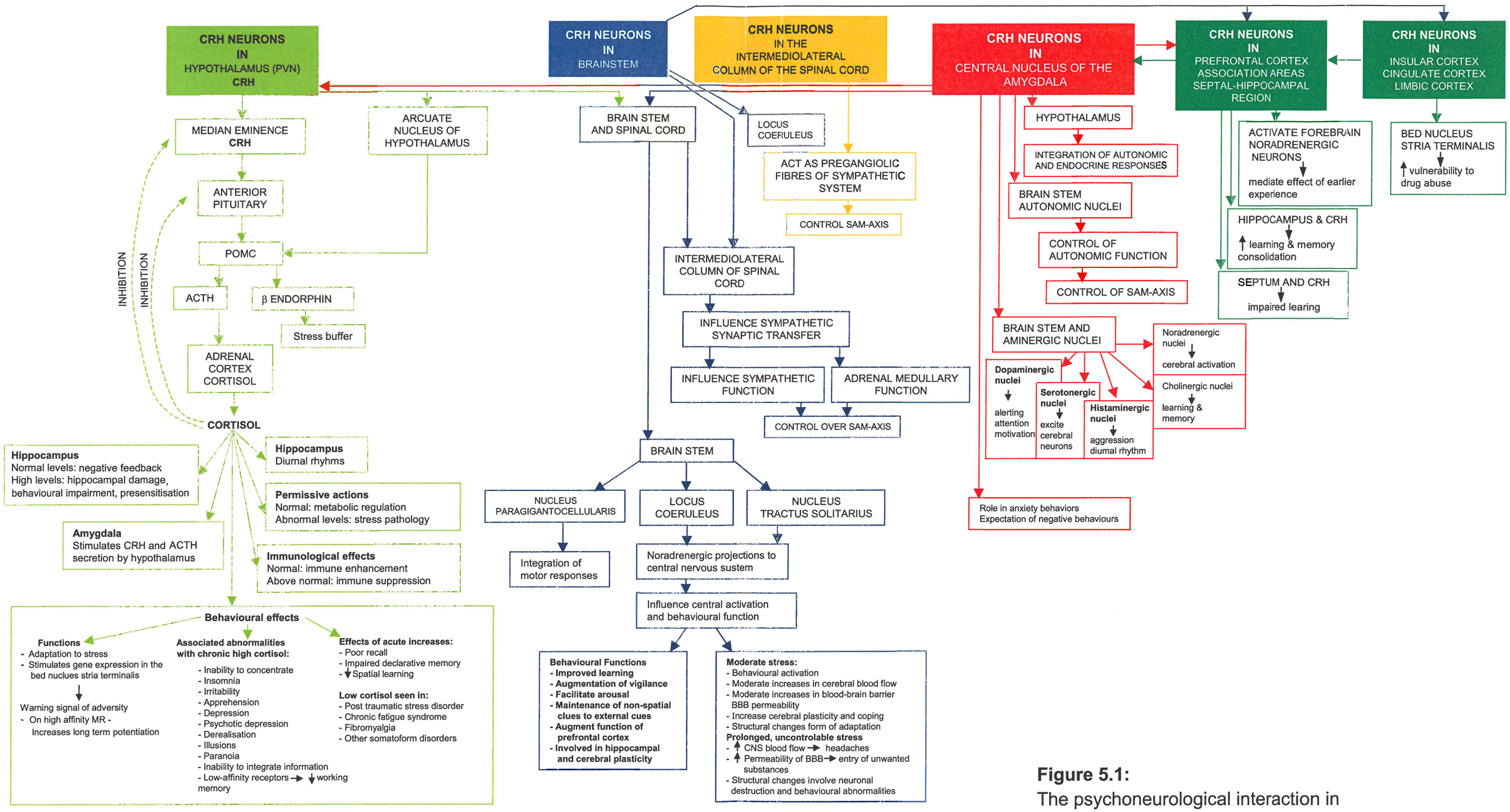
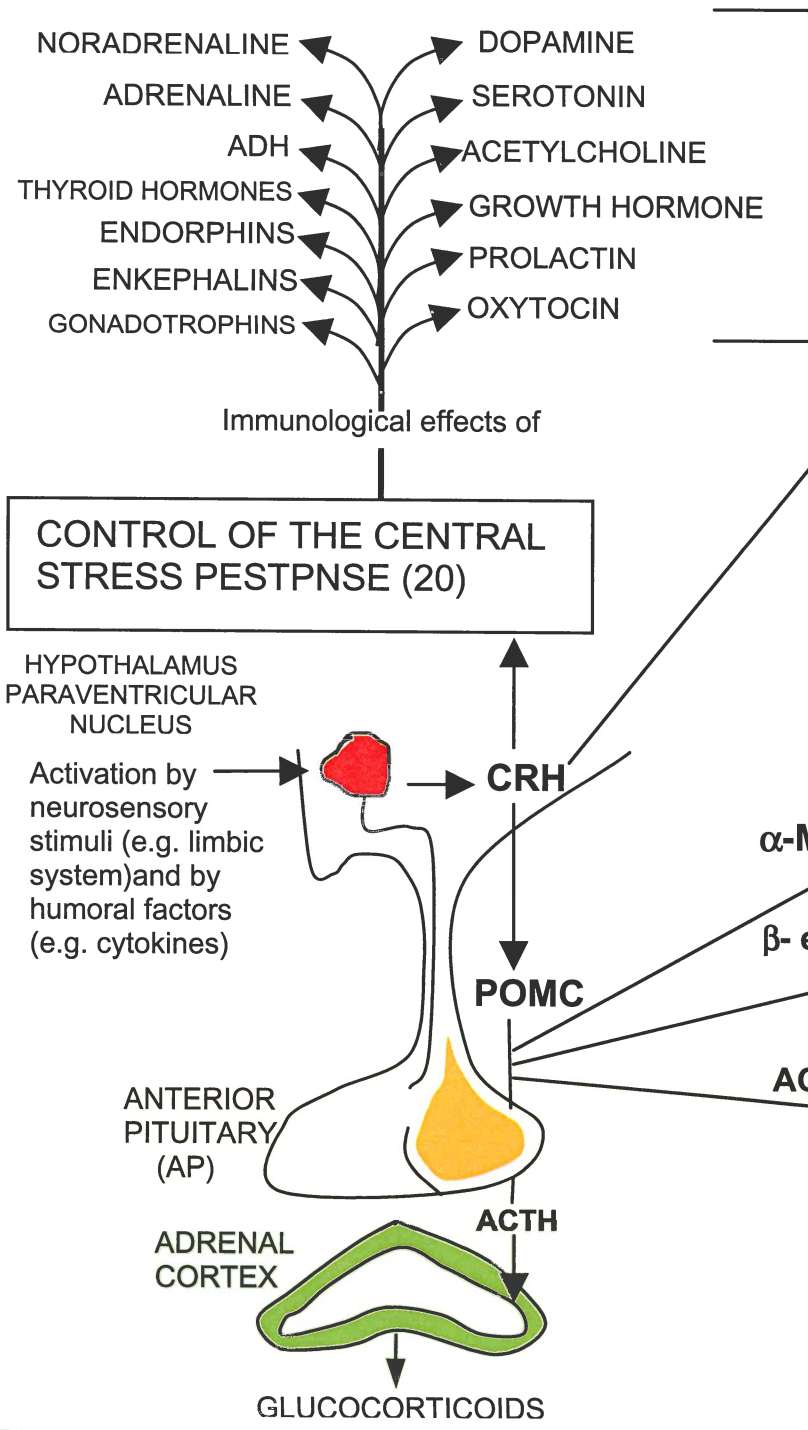


Figure 5.1:
The psychoneurological interaction in terms of the CRH/HPA-axis.
The central role of CRH in the control of the neurohormonal and behavioural stress response.

Legend to Figure 5.1

Figure 5.1: The psychoneurological interaction in terms of the CRH/ HPA-axis. The central role of CRH in the control of the neurohormonal and behavioural stress response.

[The scheme illustrates the distribution of CRH neurons throughout the central nervous system. CRH neuronal cell bodies are found in the paraventricular nucleus (PVN) of the hypothalamus. These neurons are in control of the HPA-axis and its functions. By controlling the secretion of cortisol the PVN CRH neurons indirectly control and integrate the functions mediated by cortisol, including a) the permissive functions of cortisol on metabolic regulation, b) cortisol's behavioural effects, c) its immunological effects, d) its control of the stress response through negative feedback to the hippocampus, e) its stimulatory effect on the CRH neurons of the amygdala that in turn stimulate CRH and ADH neurons of the hypothalamus and, f) the effects of cortisol on diurnal rhythms. The CRH neurons of the PVN are mainly involved with the control of peripheral stress responses. However, PVN CRH neurons also project to other areas such as the arcuate nucleus, the brain stem and the spinal cord where they help to coordinate the stress response. CRH neurons are also found in the brain stem and intermediolateral column of the spinal cord where they influence and coordinate autonomic functions, somatic motor functions and behavioural functions and from where they control the CNA/SAM-axis. The most important group of CRH neurons, with regard to behavioural functions are found in the amygdala. They project to and stimulate the activity of the PVN CRH neurons of the hypothalamus where they integrate and control autonomic and endocrine functions, project to the autonomic nuclei of the brain stem to control SAM-axis activity, and project to the aminergic nuclei of the brain stem that, in turn, project back to the cortex to control the emotional and cognitive functions of the brain. These pervasive CRH projections from the amygdala greatly contribute to the integration of the neuroendocrine, autonomic nervous system and behavioural responses during psychologically–induced stress. Clusters of CRH neurons are further found in the cerebral association areas and limbic structures that help with the analysis of information and the formation of perceptions about potential stressors.]



All with their own immunomodulatory effects

Immunological effect of CRH from immune cells and nerve endings
Control the pain of inflammation by stimulation of the local release of opioid peptides (8)
Mast cell degranulation with vasodilation, increased vascular permeability, fluid extravasation and hypotension (19)
CRH receptors on immune cells and immune accessory cells, e.g. macrophages mast cells, leukocytes, as well as inflamed synovia (19)
CRH stimulates IL-1 secretion from monocyte (19)
CRH stimulates IL-2 secretion from lymphocytes (19)
CRH stimulates IL-6 secretion from mononuclear cells (19)
CRH stimulates IL-2 receptor expression (19)
CRH enhances chemotaxis (19)
Stimulates lymphocyte proliferation (19)
CRH stimulates the production of reactive oxygen radicals by macrophages (19)
Increased hypersecretion in human autoimmune inflammatory diseases and Hashimoto's thyroiditis (19)
Inhibition of certain immune and inflammatory responses points towards a bi-phasic action

Immunological effects of α-Melanocyte stimulating hormone
Antagonises pyrogenic and pro-inflammatory response
Effects production as well as secretion of cytokines (IL-1, IL-6, TNF, IFNγ) (11)
Reduces neurogenic aspects of inflammatory response (11)

Immunological effects of β- endorphin and other opioids
Inhibitory effect on most immune functions – independent of steroids (1)
Co-factors in determining Th1-Th2 response - favours Th2 response (1)
Decreases T-lymphocyte mitogenic response, IFN secretion, expression of HLA class 11 antigens, T-cell receptor CD3 complex IL-2 receptor,

Immunological effects of ACTH
Inhibits the immediate response to injury by suppression of vascular leakage (6).
Steroidogenic effect – stimulates secretion of immune active glucocorticoids
Exerts direct immunological effects as well as indirect through neuroendocrine modulation.
Influence phagocytosis processes (cellular migration,chemotaxis, endocytosis, etc) – usually
positively, in concert with cytokines and other immune modulators (15).
Dose-dependent effect on humoral immunity, but generally inhibitory (15).

Immunological effects of glucocorticoids (cortisol)
Primary lymphoid tissues:
Role in thymic cell development, T-cell selection, apoptosis of cells in thymus (2)
Secondary lymphoid tissue:
Role in splenic T-cell selection – peripheral T-cell selection - through clonal deletion and expansion (2).
Necessary for initial antigen-specific response (2) in secondary lymphoid tissues
Total *in vivo* immune response:
Generally anti-inflammatory at pharmacological levels – immune modulatory in physiological levels
Bi-phasic response – dose-dependent and exposure time-dependent
May be a prerequisite for the coordinated immune response (5)
Plays a role in maintaining the appropriate balance between the expression of inhibitors and effectors of apoptosis of cells (12)
Basal physiological and low acute stress levels of GC, in a time, dosage, and cytokine-dependent manner can enhance almost all aspects of immune function (normal regulation and acute adaptive stress response)
During infections: Excessive pro-inflammatory cytokines will stimulate HPA-axis to increase cortisol to immune-inhibitory levels (protection of body against systemic inflammatory response, self-damage and autoimmune processes)
Pharmacological dosages: generally immune suppressive – with a shift from proinflammatory to antiinflammatory cytokine response.
Allergic reactions to corticosteroids may develop (14)
Mechanisms:
Acute stress: ↑circulating neutrophils; ↓ circulating lymphocytes (Th, Tc, B-cells, NKC), monocytes. Represent redistribution of leukocytes rather than destruction (17).
Long acute to chronic: ↓ Total leukocyte numbers.
Modulation of the immunological effects (differentiation, cell proliferation, inflammatory and immune responses) of peptide hormones, metalloproteinases and of cytokines by interfering with the activity of other transcription factors such as CREB, AP-1 and NF-κB (3).
Inhibits antigen presentation by macrophages as well as their production of IL-1, IL-2, IL-6, IFNγ (18).
Arrests lymphocyte proliferation in stage G0 and G1 (18)
Suppresses the differentiation of monocytes to macrophages (18)
Important role in Th1/Th2 response: favours Th2 cytokine responses (autoimmunity linked to Th1-responses; allergy and asthma linked to Th2-responses) (2)
Upregulation of certain cytokine receptors – enhancement of cytokine action (2)
Induction of acute phase responses – including behaviour (2)

Stimulatory effect on early B-cell responses (Th2-response) (2)
The type 1 GC receptor-cortisoi compiex acts as functional antagonist of the type 2 rece
which means that cortisol can induce opposing effects (20).
The affinity of GC receptors are determined by genetic polymorphisms, associations wit
immunophilins, and by various cytokines (20)
In inflammation:
Inhibits the immediate inflammatory response to injury by suppression of vascular leakage (6).
Many of the anti-inflammatory effects mediated through a combination of the up-regulation of anti-inflammatory mediators and the down-regulation of pro-inflammatory mediators
Binds to GRE on glucocorticoid-responsive genes and increases the transcription of genes coding for anti-inflammatory proteins (lipocortin-1, IL-10, IL-1 receptor antagonist,, neutral endopeptidases) (7)
Inhibits the expression of multiple inflammatory genes (pro-inflammatory cytokines, enzymes, receptors, adhesion molecules) through direct inhibitory interaction between activated GC receptors and activated transcription factors (7).
Can suppress gene expression of immune-related substances by changing chromatin structure (7).
Stimulates lipocortin-1 production that in turn inhibits phospholipase A_2 activity with a resultant decrease in the production of inflammatory mediators such as prostaglandins and leukotrienes (18)
Stimulates the secretion of neutrophil-derived lipocortin-1, which inhibits neutrophil extravasation in response to chemotaxic stimuli (9)
Decreases the expression of the gene that codes for cyclooxygenase-2 – thus further suppresses the production of inflammatory prostaglandins (18)
Control local inflammation through lipocortin-induced detachment of neutrophils from postcapillary venules (4).
Inhibits the gene that encodes for nitric oxide synthase (18)
Stabilises lysosomal membranes - thus reduces local release of proteolytic enzymes and hyaluronidase (18)
Inhibits the differentiation and proliferation of mast cells (18)
Suppresses the proliferation of fibroblasts, as well as their synthesis and deposition of fibrils (18)
Not only does GC regulate cytokine secretion, but cytokines modulate the function and expression of GC receptors (13)
Mediates the production of thymosin β sulfoxide by monocytes which inhibits neutrophil chemotaxis, lowers neutrophil adhesion to endothelial cells and causes neutrophil dispersion (10)
Mediates expression of adhesion molecules (glucocorticoid-induced adhesion match) through stimulation of the production of cytokines and lipocortins which control adhesion molecule expression (18)

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Figure 5.2 The neuroimmunological interaction in terms of the CRH/HPA-axis. Central role of CRH in the neurohormonal control of immunity.

Legend to Figure 5.2

Figure 5.2: The neuroimmunological interaction in terms of the CRH/ HPA-axis. The central role of CRH in the neurohormonal control of immunity.

[CRH controls the secretion of pro-opiomelanocortin (POMC) that contains within its structure β-endorphin, α-MSH and ACTH. Each of these hormones has their own immunological effects. ACTH also regulates the release of cortisol – a steroid hormone with both immuno-enhancing and immunosuppressive effects. CRH is, in addition in control of the activity of the neurohormonal factors of the central stress response. Each of these substances has either immuno-enhancing or immunosuppressive effects or both. CRH thus controls the immune system directly through its own effects on the immunological processes and indirectly a) through its control of the POMC-derived substances and the ACTH-controlled release of cortisol, as well as b) its control over the neurohormonal substances of the central stress response.]

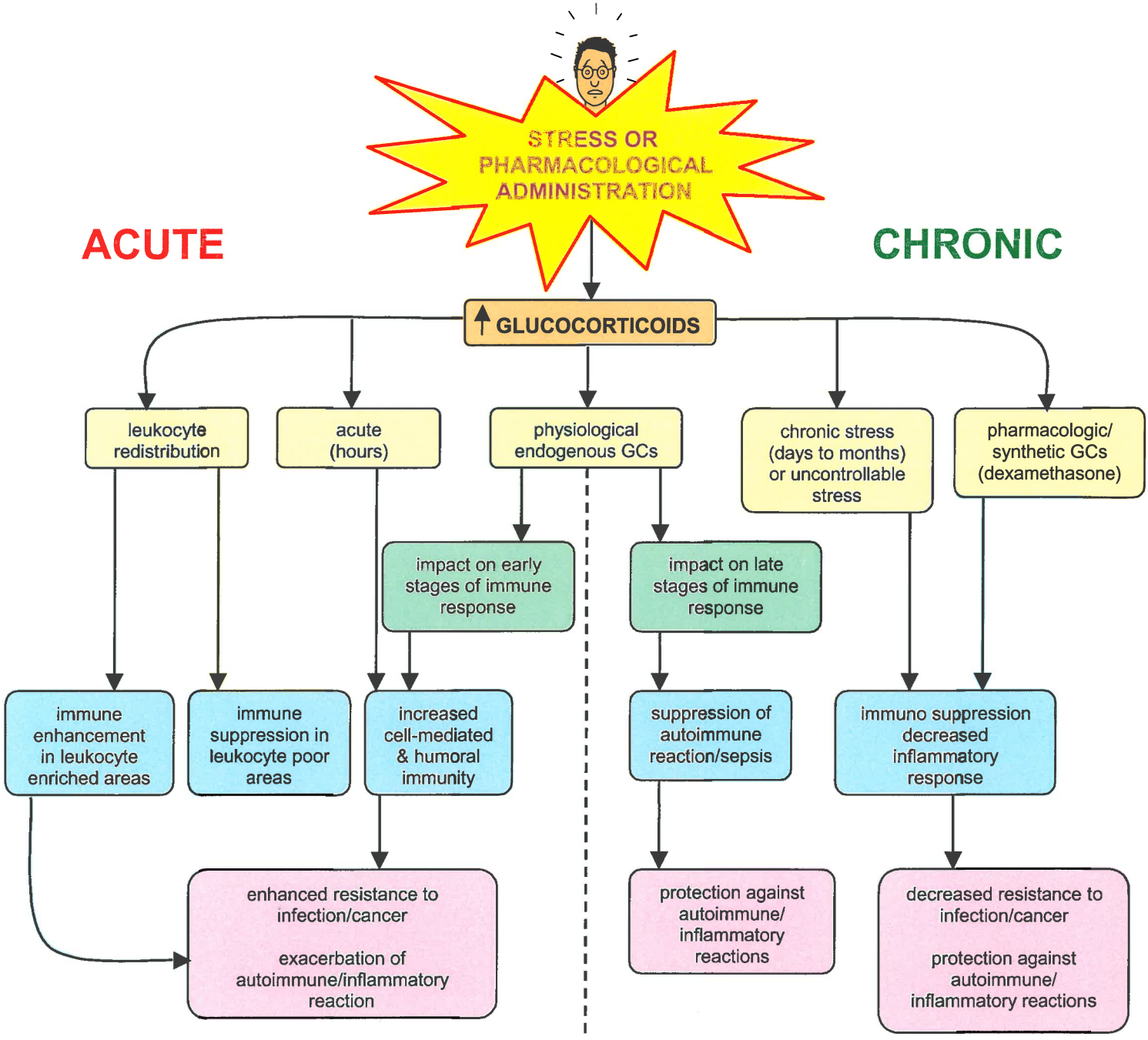

Figure 5.3 : The effects of acute and chronic increases in glucocorticoids. On the left is shown acute -induced immune enhancement, i.e., redistribution of areas where needed and a totalse in innate, humoral and cellular immunity. This seen as an adaptational response to protect the body against infections, but autoimmune and inflammatory responses.On the right is shown immune prolonged ds of stress or at pharmacological levels. This can predispose to development of cancer but offer some protection against autoimmune and

Legend to Figure 5.3

Figure 5.3: The difference between chronic and acute stress-induced stimulation of the HPA-axis.

[On the left is shown acute stress-induced immunoenhancement, i.e., redistribution of leukocytes to areas where needed and a total increase in innate, humoral and cellular immunity. This should be seen as an adaptational response to protect the body against infectious stressors, but can predispose to autoimmune and inflammatory complications. On the right is shown immunosuppression that occurs during prolonged periods of uncontrollable stress or at pharmacological levels of glucocorticoids. This can predispose to infections, allergies and cancer development, but offer some protection against autoimmune and chronic inflammatory conditions.]

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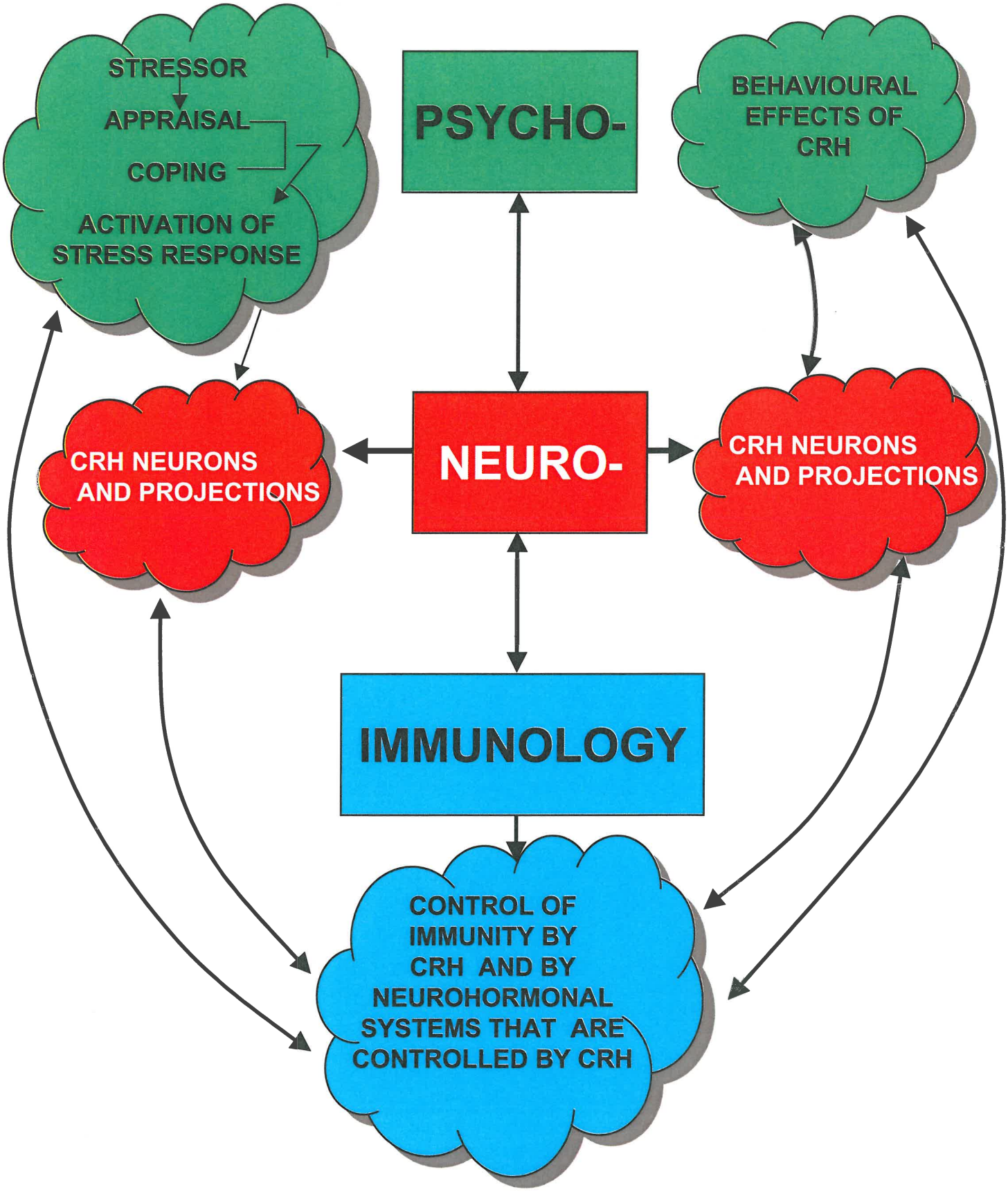

Figure 5.4 Outline of the central role of CRH in psychoneuroimmunology in terms of the CRH/HPA-axis

Legend to Figure 5.4

Figure 5.4: Outline of the central role of CRH in psychoneuroimmunology in terms of the CRH/HPA-axis

[The psychoneuroimmunological integration is shown in four layers with the top horisontal layer representing the *psycho-*, the middle layer the *neuro-* and the bottom layer the *immunological aspects*. A more detailed presentation of the psychoneuroimmunological interaction is incorporated into Figure 5.15]

5.1 The central nervous system CRH system and the central role of CRH in the neurohormonal and behavioural stress response.

The aim of this section is to show, firstly, the distribution of CRH neurons throughout the nervous system and secondly the central nervous system CRH neuronal system as integrator between the various psychological and physiological functions of the stress response. This section describes the information shown in Figure 5.1.

Around 1956 Hans Selye described the role of the hypothalamo-pituitary-adrenocortical (HPA) axis in the stress response (22). He also described the stress reaction that follows upon psychological stressors as the non-specific stress response. Although we know today that large variations in the pattern of the non-specific stress may occur, the term non-specific stress response, as coined by Selye, is still used to distinguish it from the homeostatic disturbances caused by specific stimuli where homeostasis can be returned to normal by feedback mechanisms specific for the disturbance. Perhaps it is at this stage necessary to mention that the non-specific stress response is, in contrast to the specific stress response, not a correction of the disturbed homeostasis, but rather, a new homeostasis aimed at helping to cope with the stressor. Today it has, in certain circles, become customary to refer to allostasis rather than to the non-specific stress response. Allostasis is seen as the regulation of the internal milieu through neurohormonal changes – in other words to keep internal stability through adaptational changes in the neurohormonal homeostasis (23,24). The term allostatic load can be seen as the equivalent for the description "the effects of chronic stress", i.e., it is the price the body and mind pay for containing the effects of arousing stimuli and for the anticipations of negative events (25).

Formal recognition of the relativity of the non-specificity in the so-called non-specific stress response started around 1968 with the writings of Mason (26). Mason's big problem with the theory of Selye was that only the efferent leg of the stress response was taken into consideration and that very little was said about the nature, strength and chronicity of the stimulus input (26).

Since the work of Mason many contributors have shown that the nature of the so-called non-specific stress response is determined by factors such as the context in which it occurs, the psychosocial environment, and the perception of the individual about the stressor, which, in turn, is determined by earlier cognitive and emotional experiences and genetics. In short, the major determinants would appear to be the extent to which the individual sees the situation as potentially controllable – a phenomenon largely dependent on coping skills and the need for the individual to be in control. Of the two major stress axes, activation of the HPA-axis is the least likely to have a set pattern of activation and is most probably to the largest extent influenced by the psychological factors just mentioned in the previous sentence. This would be born out by subsequent writings.

The aim of this section is to demonstrate the ubiquitous distribution of CRH neurons throughout the central nervous system, and to demonstrate the central role of CRH, the first hormone of the HPA-axis, in the stress response and in the integration of the behavioural, neuroendocrine, autonomic nervous system, somatic motor and immune responses to stress. This was summarised in Figure 5.1. The following paragraphs will provide a brief description, with the necessary references, of the information presented in Figure 5.1.

Figure 5.1 illustrates the distribution of CRH neurons throughout the central nervous system, as well as the pervasiveness of their projections – through which the CRH system coordinates and integrates the various modalities of the stress response. It has in fact been hypothesized that the major function of CRH is to regulate and coordinate the body's autonomic, endocrine, metabolic, behavioural and emotional responses to stressors (27).

Through its influence on, and control of the HPA-axis and the CNA/SAM-axis, as well as the co-operative control of the two axes on other neurohormonal systems, the CRH system occupies a central role in the stress response. The claim of the hypothesis that CRH controls the functions of the CNA/SAM-axis is supported by the results of pharmacological administration of CRH. Pharmacological administration of CRH leads to the typical "fight-or-flight" circulatory pattern (28), increased firing of the sympathetic

nerves, increased blood levels of adrenaline and noradrenaline, an increase in blood sugar (29), decreased parasympathetic activity, increased motor activity, decreased sexual drive, appetite, and water intake (27) and an increase in the firing rate of the nucleus coeruleus (30).

The distribution of CRH neurons, their projections and coordinating functions are shown in Figure 5.1. The largest collection of CRH neurons is found in the paraventricular nucleus (PVN) of the hypothalamus (20,31). These are the neurons known to initiate and regulate HPA-axis activity and which are ultimately the primary stimulators of cortisol secretion. This was shown on the left side of Figure 5.1 and the relevant section of it is reproduced at this point as Figure 5.5 - in an attempt to facilitate the reading of this section.

Figure 5.5 schematically shows that the CRH neurons of the paraventricular nucleus project to the median eminence from where the secreted CRH travels via a portal system to the anterior pituitary. In the anterior pituitary CRH stimulates the release of pro-opiomelanocortin (POMC). From the POMC molecule are derived several hormones, amongst others the adrenocorticotropic hormone (ACTH) and β-endorphin. β-Endorphin is a major stress buffer and counteracts many of the stress response reactions of the other stress hormones. ACTH travels via the circulation to the adrenal cortex where it stimulates the production and release of cortisol. The secretory activities of CRH, as well as the role of cortisol in the stress response – especially its behavioural effects - will be discussed on the next couple of pages.

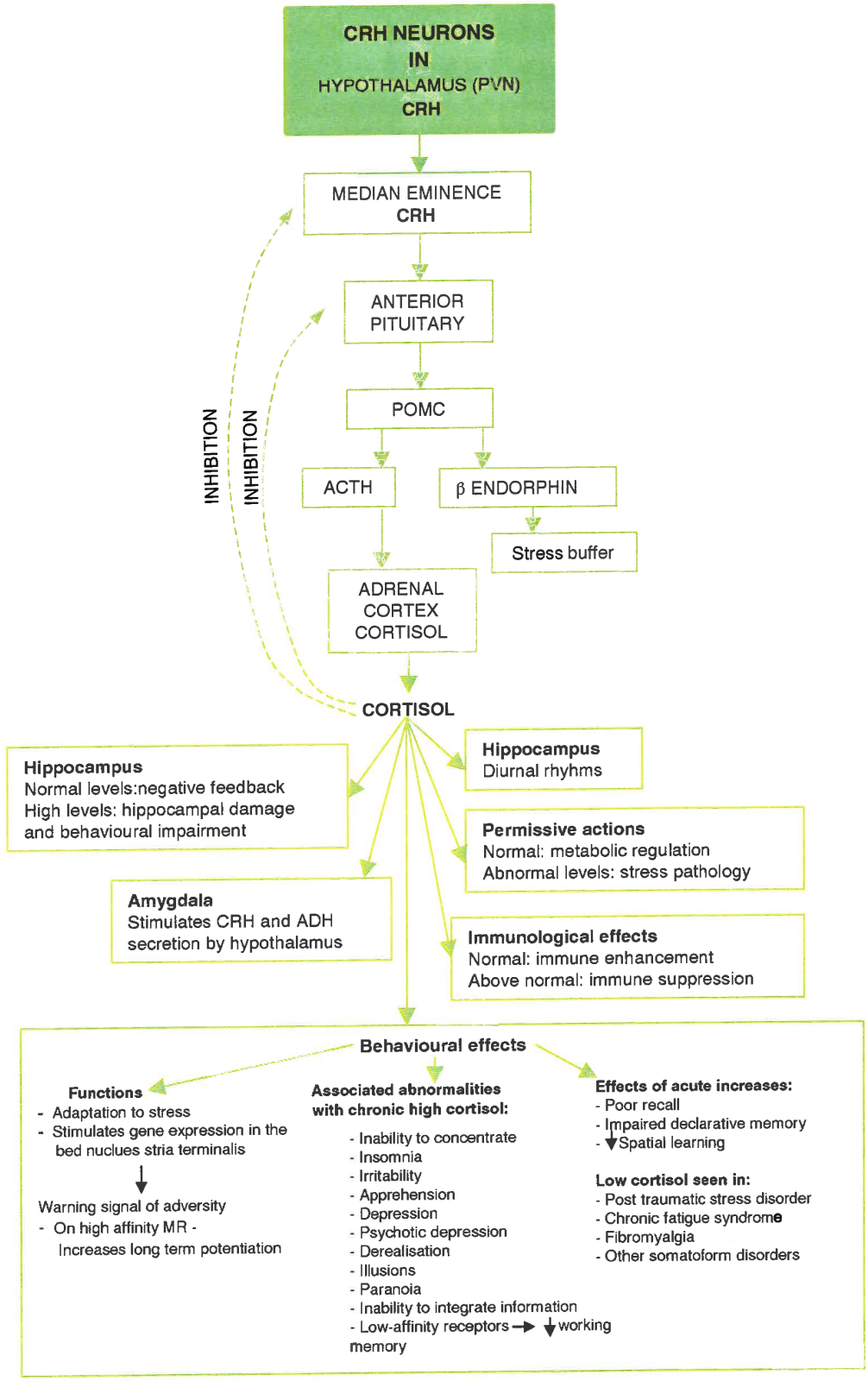

Figure 5.5: The integrative role of the paraventricular nucleus CRH neurons in the central stress response.

A number of facts should be considered when viewing these CRH neurons in terms of the stress response:

- The paraventricular nucleus (PVN) CRH neuronal activity is stimulated, to a large extent, primarily by neurosecretory stimuli from brain centra involved in higher brain functions and by humoral factors such as immune cell-derived cytokines. Peripheral sensory information reaches the PVN either via the reticular formation or via the hypothalamus to the cerebral cortex, to the limbic system – the latter of major importance with regard to CRH secretion in response to stress (32).
- The HPA-axis, which is mainly stimulated by PVN CRH activity, is under negative feedback control due to the effect of cortisol on a) the hypothalamus, where cortisol inhibits gene expression, b) the anterior pituitary, where the rate of POMC synthesis is inhibited at nuclear level and, c) at the hippocampus – where stimulation of the hippocampal cortisol receptors lead to inhibition of CRH production and CRH release from the hypothalamus (33,34,35). The effect of cortisol on the hippocampus is of great importance for the behavioural functions, as the hippocampus plays a role in long-term declarative memories, as well as in the integration of emotional and cognitive processes (36).
- The paraventricular nucleus contains neurons that secrete mainly CRH and neurons that secrete CRH, as well as ADH (20,31).
- A synergistic cooperation exists between CRH and ADH with regard to the stimulation of ACTH from the anterior pituitary and arcuate nucleus. ADH increases the effectivity of CRH by a factor four (20,31).
- The same synergism between CRH and ADH is seen with regard to the effects of CRH effects on behavioural functions (20,31).
- During prolonged stress, impulses from the amygdala cause an increase in the ratio between paraventricular nucleus neurons that secrete both ADH and CRH and neurons that secrete only CRH (20,31).
- Cortisol has a ten times stronger negative feedback on the neurons that secrete only CRH than on neurons that secrete both CRH and ADH – in fact, the negative feedback to the latter is rather weak (20,31).

- The activity of CRH during periods of prolonged stress is thus effectively several times higher during chronic stress as a result of a) the synergism between ADH and CRH, b) the stress-induced effect of the amygdala on the CRH:CRH/ADH neuronal ratio and c) the difference in the negative feedback on the two types of CRH producing neurons (20,31).
- During prolonged periods of distress the negative feedback of the high cortisol levels on the HPA-axis, via the hippocampus, is further reduced due to cortisol-induced damage to the hippocampus. The hippocampal control of the HPA-axis is the most important of the various negative feedbacks on the HPA-axis and cortisol–induced damage to the hippocampus and inhibition of hippocampal function may lead to further increases in cortisol production, adrenocortical hypertrophy and eventually damage to both the adrenal cortex and the hippocampus. The cortisol-induced hippocampal damage is accompanied by behavioural alterations such as poor explicit memory. The total picture of stress-induced hypercortisolaemia, with the accompanied hippocampal damage and memory impairment, is known as the glucocorticoid cascade hypothesis (37).

The indirect psychological, as well as physiological effects of CRH, i.e., those exerted via the HPA-axis, are extremely pervasive. Cortisol alone has several types of functions, all contributing to the integration of the stress response:

- The permissive functions of cortisol, probably the best known of its functions, are those where cortisol plays a major endocrine regulatory role in the control of metabolic processes. These effects and their contribution to psychopathological and pathophysiological processes are well known (38).
- Cortisol also plays a very important role in the control of many potentially harmful stress-related responses, in fact, cortisol is a very important factor in the adaptation to stress (31).
- It has a major impact on the diurnal rhythmicity, with alterations in its own diurnal secretory pattern seen during periods of chronic stress (31).

- It is further know that cortisol, in addition to its role as negative feedback mechanism of its own secretion via the hippocampus and hypothalamus, may also feedback to the amygdala and amygdalar outflow and to the hippocampus, i.e., to structures involved with the formation of emotions and memory (39).
- Cortisol influences behaviour in a variety of ways. Direct effects of cortisol on behaviour were published even before the 60's (32), as can be seen from reports of
  - The inability to concentrate, drowsiness, restlessness, insomnia, irritability, and apprehension reported in some patients with adrenal insufficiency
  - Reports of depression and sometimes psychosis in some patients with Addisons disease
  - Various psychological disturbances reported in a number of patients with Cushing's syndrome or with ultra-long term therapeutic administration of high dosages of cortisol, including confusion, anxiety, insomnia, delusions, hallucinations, derealisation or psychotic depression, but sometimes also the opposite such as euphoria, elation and an increase in social activity
  - Alterations in mental state upon cessation of long term steroid treatment, including illusions, paranoia, derealization and bizarre behaviour
  - Associations seen between certain mental disturbances and abnormalities of cortisol metabolism. In general it would appear that cortisol may be a factor in the exacerbation of psychological disturbances during new, aversive situations, with failure of ego defense mechanisms, ego disintegration, and loss of control. Hypocortisolaemia has been implicated as a contributing factor in the inability to selectively concentrate attention and the inability to correctly receive and integrate information – both processes of major importance in the development of appropriate perception
- More recent work further confirms a clear connection between cortisol and the behavioural functions
  - Cortisol, at chronic stress-induced levels, is now generally accepted to give rise to loss of hippocampal neurons with a loss of some of the hippocampal-associated behavioural functions (40) and memory impairment

- Occupancy of low-affinity hippocampal receptors at stress levels of glucocorticoids can lead to (41)
    a. transient reduction in long-term potentiation – perhaps giving rise to stress-induced and diurnal variations in working memory
    b. suppression of hippocampal neurogenesis
    c. atrophy of apical dendrites
- Occupancy of high-affinity mineralocorticoid receptors (MR) by low levels of glucocorticoids prolongs long term potentiation (42)
- Stimulation of the bed nucleus stria terminalis by cortisol increases CRH gene expression which signals adversity – a sort of early warning system of potential danger (43)
- Clinical correlations between high cortisol levels and cognitive impairment are seen in
    a. Cushing's disease, Alzheimer's disease, aging and depression where links were shown between cortisol-related cognitive deficits and loss of hippocampal volume (44,45,46,47,48)
    b. Childhood physical and sexual abuse, loss of hippocampal volume and cognitive deficits such as memory impairment (49)
- Acute stress-induced cortisol secretion has, in addition to the effect of long term exposure to glucocorticoids with the accompanying hippocampal damage, also been shown to impair cognitive function. The connection was seen in mental arithmic tests by an inverse correlation between cortisol response and mental performance (50), poor retention of word lists during stress-induced high cortisol secretion (51) and in impaired declarative memory and spatial learning upon cortisol administration (51). This acute effect of cortisol is in direct contrast to the cognitive enhancement of acute stress-induced catecholamine secretion, discussed in a previous chapter.

In just looking at the effects of cortisol we can already, as shown in the previous pages, see how CRH, via its cortisol-stimulating effect, can integrate endocrine, metabolic, diurnal, stress regulatory and behavioural functions. The influence of the paraventricular

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nucleus CRH neurons is, however, much more pervasive than that mediated through its control of the HPA-axis functions and cortisol secretion. Additional effects, as will be seen in the following paragraphs, are mediated via projections from the paraventricular nucleus CRH neurons to the arcuate nucleus, the brain stem and the intermediolateral column of the spinal cord. The section of Figure 5.1 that deals with these projections is reproduced below as Figure 5.6.

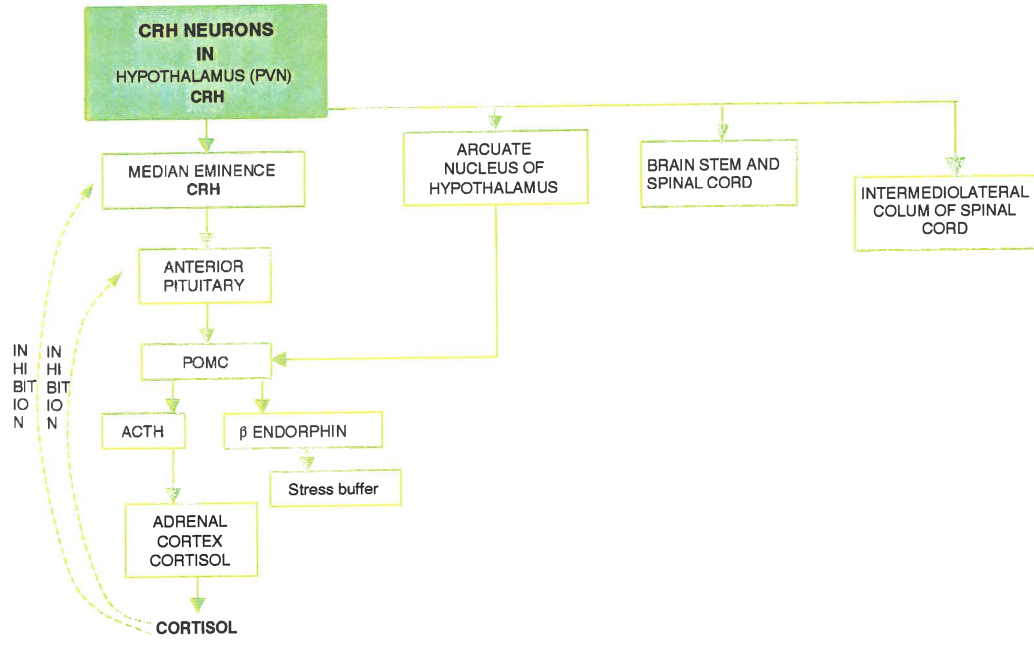

Figure 5.6: CRH projections from the paraventricular nucleus (PVN) CRH neurons of the hypothalamus to the arcuate nucleus, brain stem and intermediolateral column of the spinal cord

CRH projections from the paraventricular nucleus to the brain stem synapse with a) the nucleus paragigantocellularis, through which they influence functions such as the integration of motor responses associated with the nucleus paragigantocellularis, b) the nucleus tractus solitarius, which is involved with sympathetic regulation of cardiovascular responses and c) the locus coeruleus, i.e., the major brain stem noradrenergic nucleus from where fibres project to, and activate virtually all areas of the central nervous system. The noradrenergic fibres from the locus coeruleus is a major source of cerebral activation, as well as an important factor in mood determination (32,52). These projections thus represent indirect CRH effects on CNS activation. These detailed interactions of CRH neurons with brain stem nuclei are shown in Figure 5.1 and Figure 5.7.

CRH projections from the paraventricular nucleus, also reach the intermediolateral column of the spinal cord where the cell bodies of the preganglionic sympathetic neuronal fibres are located. By influencing the transfer of information in the intermediolateral column, CRH can virtually affect sympathetic functions throughout the body – including the secretory activity of the adrenal medulla. The sympathetic nervous system can further be influenced by CRH due to the fact that some of the preganglionic neurons are in fact CRH neurons. These are just two of the possible ways in which the HPA-axis can regulate functions of the SAM-axis. Another example, previously mentioned, is through projections to the brain stem autonomic nuclei. It is in fact now known that CRH can produce all the physiological characteristics of the "fight-or flight" response, i.e., the typical SAM-axis stress response (20,31,53).

In addition to the CRH projections to the brain stem, clusters of CRH neuronal cell bodies can also be found in the brain stem (Figure 5.1 and Figure 5.7 on the next page). These neurons project to the intermediolateral column of the spinal cord grey matter where they, as mentioned before, influence the peripheral SAM-axis functions. This is accomplished by influencing the transfer of information to the preganglionic sympathetic fibres situated in the intermediolateral column of the spinal cord. Projections from the brain stem CRH neurons also go to the prefrontal cortex, i.e., the supramodal association

areas involved in higher cognitive functions such prolonged thought processes, the elaboration of thought, working memory and other higher cognitive functions, as well as to other cerebral association areas where CRH influences the processing of information and the perceptions. A third important area which receives projections from, and is influenced by CRH projections from the brain stem is the limbic system, especially areas such as the insular cortex - an area necessary for unimodal association involving somesthetic information, the cingulate cortex – an area also involved in unimodal associations, and the hippocampus – an area of great importance for long-term declarative memory (20,32).

The brain stem CRH influence on the behavioural functions are further extended by the stimulatory effect of CRH on the brain stem locus coeruleus neurons– the major group of central nervous system noradrenergic (CNA) neurons (see Chapter 3 for references). These neurons, as well as their functions and interactions with other neuronal systems of the brain were discussed in great detail in chapter 3. Some of the behavioural functions of the central noradrenergic system are summarised in Figure 5.7. It is shown that moderate controllable stress leads to adaptational changes in the brain, as well as to increases in adaptational plasticity of the noradrenergic system. Uncontrollable stress, in contrast will generally lead to negative effects on the brain and noradrenergic system.

In looking at the appropriate section of Figure 5.1, as reproduced on the next page as Figure 5.7, it should be clear that the brain stem CRH neurons and its projections can help to integrate and coordinate the behavioural functions, CNA/SAM-activity, and motor functions of the stress response.

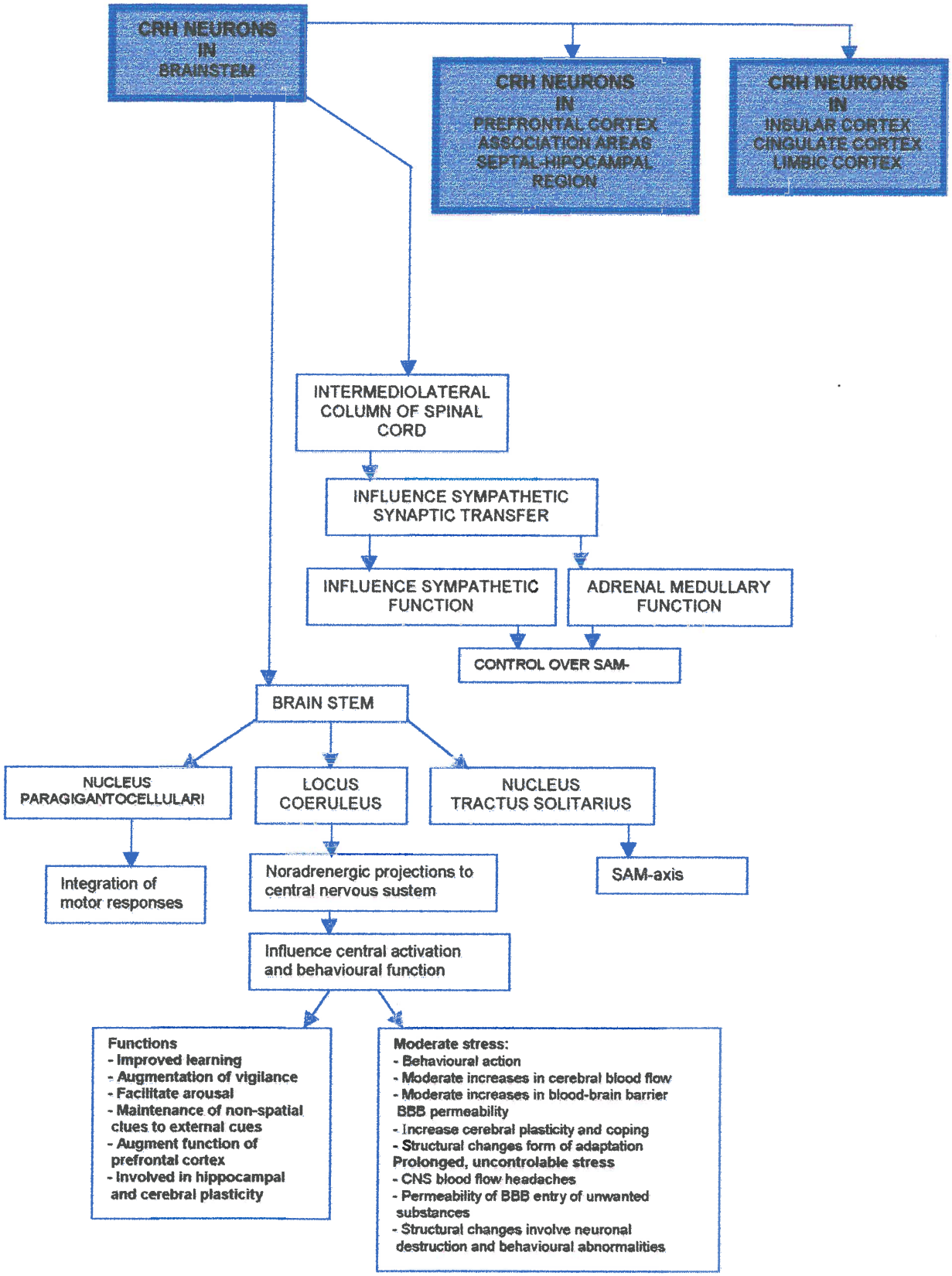

Figure 5.7: Distribution of CRH neurons in the brain stem and their projections

The major CRH neurons, with regard to the behavioural responses are found in the amygdala (54). These neurons are of great importance during the stress response where they play a role in the integration of autonomic, neuroendocrine, and behavioural responses to stress. The responses that occur upon stimulation of the amygdala are very similar to those seen upon central CRH injections. During conditions of emotional stress amygdalar CRH neurons are known to be stimulated to increase their CRH output and similar responses are seen in the amygdala upon central CRH injections (20,31,54). The appropriate part of Figure 5.1 showing amygdalar and other cerebral CRH nuclei is seen below as Figure 5.8. The discussion of Figure 5.8 follows on the next pages.

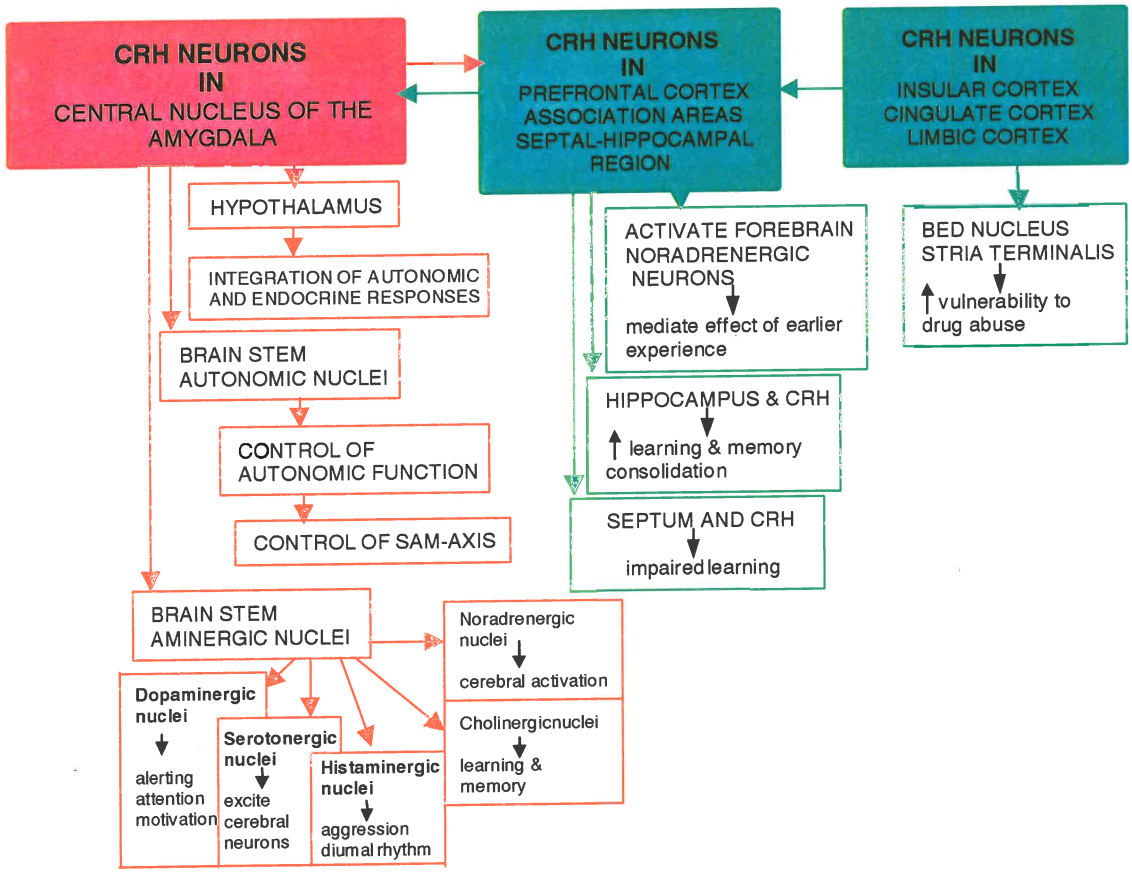

Figure 5.8: CRH neurons and their projections in the amygdala and other structures involved with emotional and cognitive processes

Upon stressor-induced stimulation of the amygdala impulses are sent, as previously mentioned, to the paraventricular nucleus of the hypothalamus to increase the number of neurons that secrete both CRH and ADH. This will strengthen the CRH-induced ACTH-stimulating effect with an increase in cortisol and cortisol-related functions as well as the CRH-induced behavioural effects. During the central stress response integrated information from the amygdala is also sent, as shown in Figure 5.8, to areas of the hypothalamus, brain stem autonomic nuclei, brain stem aminergic nuclei, cerebral association areas, and limbic system, to coordinate the stress response. The importance of the CRH neurons of the amygdala in the coordination of the stress response is that the amygdala receives integrated information from the prefrontal cortex and limbic system, areas of great importance for analysis of incoming information, for the elaboration of thought and the development of perceptions. Information from the amygdala is subsequently sent to the brain stem and hypothalamus. Impulses from the hypothalamus and autonomic nuclei of the brain stem control almost all peripheral aspects of the stress response, while impulses from the aminergic nuclei of the brain stem control the activation state of the cerebral cortex and underlie most mood states (20,31,54). The CRH projections from the central nucleus of the amygdala go to the bed nucleus of the stria terminalis, the lateral hypothalamus, the midbrain central grey, the raphe nuclei, the parabrachial region and the nucleus tractus solitarius. Amygdaloid CRH neurons that project directly to dopaminergic, noradenergic, cholinergic, histaminergic and serotonergic neurons of the brain stem (54) are of great importance in setting the mood and activation state of the cerebral cortex during the stress response. The behavioural functions of the aminergic nuclei were shown in Figure 3.6 of the chapter which dealt with the psychoneurological interaction in terms of the central noradrenergic system, i.e., Chapter 3. To stress the importance of these CRH connections from the amygdala, a structure strongly associated with emotion and implicit memory, and the brain stem aminergic nuclei, it is perhaps necessary to recap some of the major functions of the aminergic nuclei. These nuclei project back to the higher brain centra and serve as major neuroendocrine regulators (55) in that

- the nigrostriatal dopaminergic system, which amongst others responds to aversive, as well as to appetitive information, is involved in attention, motivation and in alerting the individual.
- the raphe nuclei or brain stem serotonergic system, that increases the excitability of its target neurons which may explain why the system is often associated with depression.
- the basal nucleus of Meynert or acetyl cholinergic system, which is strongly associated with learning and memory.
- the tuberomammillary nucleus or histaminergic system, known to act asymetrically with regard to the hemispheres, and which is implicated in aggressive behaviour, circadian rhythms and abnormalities such as catalepsy

It is highly likely that CRH fibres from the amygdala also innervate CRH neurons in most of the areas to which they project, and that the CRH neurons of these areas project back to the amygdala (54). The amygdala is thus part of a network of brain nuclei that forms the basis of the stress response and that are interconnected by CRH neuronal pathways (54).

Indications are that major functional differences exist between the CRH neurons of the amygdala and that of the paraventricular nucleus. The paraventricular nucleus CRH neurons are under negative feedback control of the glucocorticoids, while in the case of the amygdalar CRH neurons, as well as those of the lateral bed nucleus of the stria terminalis, this is not the case and the regulation of CRH gene expression can be dissociated from that of the paraventricular nucleus (56). The CRH neurons of the amygdala are thought to be involved with fear and anxiety and in a number of clinical syndromes such as melancholic depression, excessive shyness and fearfulness in children, the posttraumatic stress syndrome, anticipatory anxiety, and self-administration of psychotropic drugs (56).

The prefrontal cortex, the cingulate cortex, the insular cortex, and other association areas, as well as the limbic system, also contain clusters of CRH neuronal cell bodies - in

addition to the CRH projections received from the brain stem and amygdala. These neurons, in turn, project, amongst other to the central nucleus of the amygdala. The association between these areas and the amygdala are important in the formation of emotional responses and in the appraisal of external events and internal sensations. CRH projections between the central nucleus of the amygdala, the lateral nucleus of the amygdala, the septum, the bed nucleus of the stria terminalis and the hippocampus help to integrate their individual contributions to the central stress response (20,31). The CRH neurons also activate forebrain noradrenergic activity, a pathway involved in the effect of early life experiences on adult behaviour (57). Another interesting collaboration between cortical/limbic system structures and CRH is that the effect of CRH on hippocampal neurons which would appear to be the enhancement of learning and memory consolidation – this is apparently accomplished through CRH1 receptors (58). In contrast to the effect on the hippocampus, the effect of CRH on the septum is to impair learning. At very high concentrations CRH will not only impair learning, but would cause severe anxiety. These effects are mediated via CRH2 receptors (58). When excessive CRH is associated with the development of anxiety it generally occurs when acting in collaboration with amygdaloid structures. It is, however, likely that some minimal level of preconditioned fear must be present for CRH to exert its anxiogenic effect (59). CRH, and its effects on cerebral structures involved in cognition and emotion, are implicated in a variety of abnormal behaviours. An in depth discussion of this would, however, require a thorough knowledge of the various CRH receptor type and their functions.

The preceding paragraphs showed the distribution of CRH neurons and their projections throughout the central nervous system, as well as their integrative functions. The next section will deal with the central corticotropin-releasing hormone/hypothalamo-pituitary-adrenocortical axis and immunity.

5.2 The neuroimmunological interaction in terms of the CRH/HPA-axis. The central role of CRH in the neurohormonal control of immunity

The influence of the hypothalamo-pituitary-adrenocortical (HPA) axis on the immune system is generally accepted. The knowledge of most people does, however, begins and ends with the effects of the final effector hormones, i.e., the glucocorticosteroids, on immunity. Even with regard to the effects of the glucocorticosteroids there are many misapprehensions. The most obvious mistake made is to see these steroid hormones only as immunosuppressive while, at basal physiological concentrations, they are necessary for normal immunocompetence. Another mistake is to see the glucocorticoid hormones as the only immunologically active substances of the CRH/HPA-axis.

The integrated scheme of CRH in immunological context was presented at the beginning of the chapter as Figure 5.2. The hormones of the HPA-axis consist of the hypothalamic-derived corticotropin-releasing hormone (CRH), which stimulates the release of pro-opiomelanocortin (POMC) from the anterior pituitary and other nuclei. POMC contains several hormones within its structure. Among the more important of these are β-endorphin, MSH and the adrenocorticotropic hormone or ACTH. ACTH, in turn, stimulates the release of the glucocorticoids from the adrenal cortex – the major glucocorticosteroid hormone in man being cortisol (60). The physiological-anatomical relationship of the HPA-axis can be seen in Figure 5.9 – a subdivision of Figure 5.2.

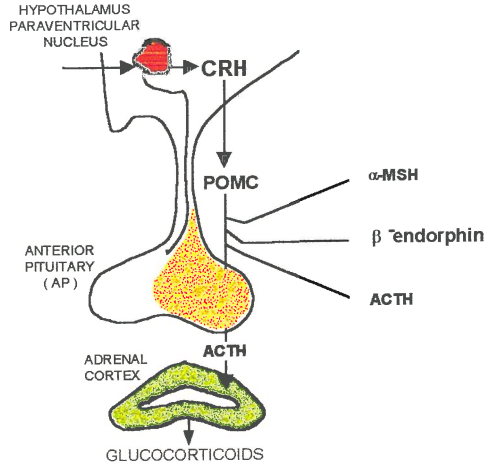

Figure 5.9: The CRH/HPA-axis

The aim of this section of the chapter is to demonstrate the influence of the CRH/HPA-axis on immunity, and more specifically the central neurohormonal role of CRH in immunological homeostasis. This was presented schematically in Figure 5.2. Before discussing this a few facts should be noted. The concept that the major stress axes, and in this case the CRH/HPA-axis, are generally immunosuppressive is, as was previously mentioned, evolutionary unsound and derived from experiments in which the effects of pharmacological dosages of steroids were tested and where synthetic steroids such as dexamethasone, rather than cortisol, were used. Cortisol has, in fact, immune-enhancing as well as immunosuppressive effects. It is, however, also important to remember that cortisol is just one of the CRH/HPA-axis hormones and that the ultimate influence of the CRH/HPA-axis is a function of the immunological effects of the total spectrum of hormones of the axis.

CRH is the first hormone of the cascade and as such the main regulator of the secretion of all other hormones of the CRH/HPA-axis, including the POMC-derived β-endorphin, MSH and the adrenocorticotropic hormone or ACTH, as well as the adrenocortex-derived cortisol. CRH, as well as the hormones derived from the mother compound POMC, are immunological active in their own right. CRH, the first hormone of the HPA-axis, can, as seen in the first section, underlie the total central stress response, i.e., it has a regulatory influence on virtually all neurohormonal factors that form part of the response. Neurohormonal substances that form part of the central stress response include the gonadotropins, thyroid hormones, noradrenaline, serotonin, acetyl choline, dopamine, β-endorphins, and other opioids, growth hormone, insulin, and others. All of these substances have immunological effects (61,62). Thus, as major regulator of the central stress response, including the activity of the CNA/SAM-axis and the CRH/HPA-axis, CRH can influence the immune system

- directly, through what appears to be mainly its pro-inflammatory actions
- indirectly, by changing the activity-level of the hormones of the HPA-axis
- indirectly, by its control over the SAM-axis. (Chapter 4 dealt exclusively with SAM-axis immune function.)

- indirectly, due to its control over a wide spectrum of neurohormonal factors that form part of the central stress response – each of them known to have immune-related effects.

It is therefore warranted to ascribe a central role to CRH in the immunological adaptation of the stress response.

The previous paragraph summarised the central role of CRH in the neurohormonal control of the immune system. In the following paragraphs the roles of the individual neurohormonal factors mentioned are briefly touched upon. This is done merely to substantiate the claim made that CRH fulfills a central role in stress-induced neuroendocrine regulation of immune function.

5.2.1 Cortisol as immunological regulator

As cortisol is generally seen as the major, and by some less informed individuals, as the only, immunologically active substance of the HPA-axis, it will be the first hormone to be addressed. Cortisol is well known for its immunosuppressive effects and is often assumed to be only immunosuppressive. The reason why cortisol is, in an immunological sense, the best known hormone of the HPA-axis is that it belongs to a class of steroids often used, in pharmacological dosages, for immune suppression after organ transplantation and in chronic inflammatory conditions such as rheumatoid arthritis. This idea of cortisol being only immune suppressive is again one of the major misconceptions about the HPA-axis and its effects on immune function – a misconception that can have seriously deleterious effects in its therapeutic applications. Cortisol is, in fact, necessary for normal immunocompetence and it is would appear to be immune suppressive mainly at pharmacological levels and at the levels seen in chronic aversive stress situations. Several good reviews on the immune modulating (63,64) and immunoenhancing (65) influences of cortisol can be found and this will not be discussed here in any great detail.

The overall effects of cortisol (glucocorticoids) were presented in Figure 5.1 and the relevant section of Figure 5.2 is presented below as Figure 5.10.

GLUCOCORTICOIDS

Immunological effects of glucocorticoids (cortisol)

Primary lymphoid tissue

Role in thymic cell development, T-cell selection, apoptosis of cells in thymus (2).

Secondary lymphoid tissue

Role in splenic T-cell selection – peripheral T-cell selection through clonal depletion and expansion (2). Necessary for initial antigen-specific response (2) in secondary lymphoid tissue.

Total in vivo immune response

Generally anti-inflammatory at pharmacological levels – immune modulatory at physiological levels. Biphasic response – dose-dependent and exposure time-dependent. May be a prerequisite for the coordinated immune response (5).
Plays a role in maintaining the appropriate balance between the effectors and inhibitors of apoptosis of cells (12).
Basal physiological and low acute stress levels, in a time-, dosage- and cytokine-dependent manner, can enhance almost all aspects of immune function (normal regulation).
During infections: Excessive pro-inflammatory cytokine production will stimulate HPA-axis to increase cortisol release to immune inhibitory levels (protection of body against infection, systemic inflammatory response, self-damage and autoimmune processes).
Pharmacological dosages: Generally immune suppressive, with a shift from pro-inflammatory to anti-inflammatory cytokine production. Allergic reactions to corticosteroids may develop (14).

Mechanisms

Acute stress: Increased circulating neutrophils; decreased circulating lymphocytes (Th, Tc, B-cells, NKCs,) and monocytes. Represent redistribution of leukocytes rather than destruction (17).
Long acute to chronic stress: Decreased total leukocyte numbers. Modulation of immunological effects (differentiation, proliferation, inflammatory and immune responses) of peptide hormones, metalloproteinases and cytokines by interfering with the activity of other transcription factors such as CREB, AP-1 and NKκB (3). Inhibits antigen presentation by macrophages, as well as their production of IL-1, IL-2, IL-6, IFNγ (18).
Arrests lymphocyte proliferation in stage G0 and G1 (18).
Suppresses the differentiation of monocytes to macrophages (18).
Important role in Th1/Th2 response: Favours the shift to a Th2 cytokine response (autoimmunity linked to Th-1 responses; allergy and asthma linked linked to Th-2 responses) (2).
Upregulation of certain cytokine receptors and enhancement of related responses (2).
Induction of acute phase responses – including behaviour (2).
Stimulatory effect on B-cell responses (Th-2 responses) (2).
The type 1 GC receptor/cortisol complex acts as functional antagonist of the type 2 receptor which means that cortisol can have opposing effects (20).
The affinity of GC receptors are determined by genetic polymorphism, associations with immunophilins, and by various cytokines (20).

Immunological effects of glucocorticoids (cortisol) - continued

In inflammation

Inhibits the immediate inflammatory response to injury by suppression of vascular leakage (6). Many of the anti-inflammatory effects are mediated through a combination of the up-regulation of anti-inflammatory mediators and the down-regulation of pro-inflammatory mediators. Binds to GRE on glucocorticoid responsive genes and increases the transcription of genes coding for anti-inflammatory proteins (lipocortin-1, IL-10, IL-1receptor antagonist and neutral peptidases) (7).
Inhibits the expression of multiple inflammatory genes (pro-inflammatory cytokines, enzymes, receptors, adhesion molecules) through direct inhibitory interaction between activated GC receptors and activated transcription factors (7).
Can suppress gene expression in immune-related substances by changing chromatin structure (7).
Stimulates lipocortin-1 that in turn inhibits phospholipase A2 activity with a resultant decrease in the production of inflammatory mediators such as prostaglandins and leukotrienes (18).
Stimulates the secretion of neutrophil-derived lipocortin-1which inhibits extravasation in response to chemotactic stimuli (9).
Decreases the expression of the gene that codes for cyclo-oxygenase 2, thus further suppresses the production of inflammatory prostaglandins (18).
Controls local inflammation through lipocortin-induced detachment of neutrophils from post-capillary venules (4). Inhibits the gene that encodes for nitric oxide synthase (18).
Stabilises lysosomal membranes, thus reducing local release of proteolytic enzymes and hyaluronidase (18).
Inhibits the differentiation and proliferation of mast cells (18). Suppresses the proliferation of fibroblasts, as well as their synthesis and deposition of fibrils (18). Not only does GC regulate cytokine secretion, but cytokines modulate the function and expression of GC receptors (13).
Mediates the production of thymosin-β-sulfoxide by monocytes that inhibits neutrophil chemotaxis, lowers neutrophil adhesion to endothelial cells and causes neutrophil dispersion (10).
Mediates expression of adhesion molecules (glucocorticoid-induced adhesion match) through stimulation of the production of cytokines and lipocortins that control adhesion molecule expression (18).

Figure 5.10: The role of cortisol in the neurohormonal control of immunity

A number of immunological effects of stress-induced cortisol secretion should be mentioned as these facts are of importance for any individual who attempts to understand the influence of the psychological disposition on the immune system. This is especially important as acute and chronic emotional stress may have direct opposite influences on the immune system. It should, however, be remembered that the *in vivo* effects are often a reflection of the combined action of both major stress axes – a fact that is perhaps of lesser importance as the SAM-axis is under strong CRH influence, as was discussed in the first section of this chapter.

The first aspect to be addressed is the significant decrease in numbers of almost all circulating leucocytes with acute stressor application. This was previously seen as immune suppressive. It is, however, now realised that it merely represent a functional redistribution of these cells from the circulation to organs such as lymphoid tissues, mucosal sites and the skin. This is, in other words, an adaptative mechanism of physiological significance where immunocompetent cells are directed to areas of defense and immunosurveillance. Upon the disappearance of the acute stressor these cells return to the circulation and it is mostly only with chronic stress, where the glucocorticosteroid levels remain above basal levels for a significant amount of time, that glucocorticosteroid-induced apoptosis with an absolute reduction in cell numbers will occur (66). Research on these aspects has even solved the riddle of how these cells are transiently removed from the circulation and sequestered in distant organs and structures through the expression of cytokine-induced expression of adherence molecules. This aspect would, however not further be addressed here. In addition to cellular redistribution, the immuno-enhancement of innate immune functions has further been verified by reports of the glucocorticoid's ability to increase the expression of pro-infammatory cytokines (IL-6, TNF, IL-6, MIF) receptors, the induction of acute phase proteins, serum amyloid A-3 mRNA levels, certain complement fractions and a decrease in the endogenous IL-1 receptor antagonist. A link between the effect of cortisol on acute phase proteins and psychological conditions such as depression has also been shown by several groups (67), but would be addressed at a later stage.

The second aspect to be mentioned is the immune-enhancing effect of cortisol on both cellular and humoral immune function by acute stress-induced activity of the HPA-axis. In addition to the functional cellular redistribution during acute stress it is now becoming evident that many immune functions are enhanced by acute stressors, including delayed type skin hypersensitivity reactions, the primary and at times even the secondary immune responses, mitogen and anti-T cell receptor-induced proliferation of splenocytes, as well as secretion of nitric oxide, IL-1β and TNF-α (68). A very clear indication that the glucocorticoids could be immune enhancing is the fact that low levels of cortisol is necessary for antibody production in *in vitro* cell cultures, and that the variability of the cortisol concentration in different batches of serum may give rise to *in vitro* variability in antibody production (69). One of the more interesting effects of glucocorticoids on the enhancement of immune function is its synergistic action with cytokines. These effects would not be described here but it is of importance to remember when, at a later stage the behavioural-cytokine interaction is discussed as both cortisol and cytokines have several behavioural effects.

The immune-enhancing effects of the glucocorticoids are probably best illustrated by practical examples such as the fact that administration of physiological dosages of glucorticoids reduces the number of respiratory infection in patients with adrenocortical insufficiency, reduces the symptoms of respiratory illness when introduced at the onset of the disease, increases the resistance to influenza virus, can be effective in cases of mononucleosis and can sometimes exacerbate inflammatory responses (67). The functional implications of the stress-induced enhancement of immunoreactivity could obviously also include beneficial effects in conditions such as cancer and infection. However, it could have seriously deleterious effects during autoimmune and chronic inflammatory conditions. A typical case of the latter is the negative effects of day-to-day acute stressors on rheumatoid arthritis (70), and on the onset and exarcerbation of psoriasis and perhaps in multiple sclerosis (71).

In contrast to the just mentioned immune-enhancing effects, the immunosuppressive effects of glucocorticoids are much better known – mainly because glucocorticoid

hormones are, in pharmacological dosages, widely used as immunosuppressive agents. The immunosuppressive effects of pharmacological administered glucocorticoids are widely reviewed and described in textbooks. Some of the effects include suppression of the synthesis or secretion of immunoglobulins, prostaglandins, leukotriens, histamine, cytokines, reactive oxygen species, as well as suppression of almost all macrophage functions, mitogen and antigen lymphocyte proliferation, NK cell activity and leukocyte migration and activation (67). Perhaps of more importance is the fact that variations in the physiological levels, specially increases above the normal physiological levels, can also have immune suppressive effects. These changes in physiological levels of endogenous glucocorticoids usually have protective effects such as a) the containment of ongoing immune responses to prevent tissue damage (72), b) helping to control the inflammatory response in order to prevent development of the systemic inflammatory response or even septic shock (the latter function mediated through the inhibition of toxin-induced increases in the production of pro-inflammatory cytokines such as IL-1 and TNF, and the inhibition of the production of eicosanoids and other inflammatory substances (67), and c) the prevention of autoimmune disease. Hypoactivity of the HPA-axis has, in fact, in the past been seen as a predictor of the development of certain autoimmune disorders (73). This protective effect against the development of autoimmune disease is mediated partially by shifting the immune response to a Th2 cytokine reponse. Of interest is the fact that individuals with a strong HPA-axis response to environmental stressors may be more resistant to the development of autoimmune disorders and there are suggestions that these individuals may perhaps be more susceptible to infections or the development of cancer. Cancer-associated personality types have been described in Chapter 2. The fact that chronic stress-induced hyperactivation of the immune system would lead to immune suppression and can be deleterious to health is indisputable. The reason why it could increase the susceptibility to infections and cancer but ameliorate autoimmune disorders and chronic inflammatory conditions is self-evident. Several good reviews on the immune suppressive effects of chronic stress are available (74,75,76).

From a psychological point of view it is important to mention that cortisol influences the type of cytokines to be produced by immune and other cells. This will not only determine the direction of the immune response but will also largely be responsible for the type of immunologically-induced behavioural adaptations of the stress response. The effect of immune-derived cytokines on behaviour will be addressed in Chapter 6. Suffice at this stage to say that cortisol favours the production of Th2 cell cytokines such as IL-4, IL-5, IL-10 and IL-13 and tends to suppress Th1 associated cytokines (76).

Many paradoxical reports and observations still exist with regard to the interaction between psychologically stress-induced glucocorticoid secretion and the immune system. A reasonable model of this interaction has been proposed by Dhabhar and McEwen (67). An adaptation of this model is seen in Figure 5.3, as presented at the beginning of the chapter. In looking at Figure 5.3 it is important to understand the difference between the effects of periods of chronic and of acute stress on the immune system. The reason is that it may very well explain the paradoxical immune-related differences in behavioural and psychosomatic symptoms seen during conditions of aversive emotional experiences.

5.2.2 Other hormones of the HPA-axis as immune regulators

CRH stimulates the release of POMC from the anterior pituitary and arcuate nucleus. Within POMC are contained several immunoregulatory hormones which, when released from the mother molecule through proteolytic processes, can exert immunological effects. The more important of these are ACTH, β-endorphin and α-melanocyte stimulating hormone. Some effects can be seen in Figure 5.1. Suffice to say that ACTH can exert both inhibitory and stimulatory influences and that, β-endorphin and α-melanocyte stimulating hormone are at present generally seen to be immune suppressive.

The relevant part of Figure 5.2, is reproduced here as Figure 5.11 in order to show some of the immunological effects of the hormones just mentioned.

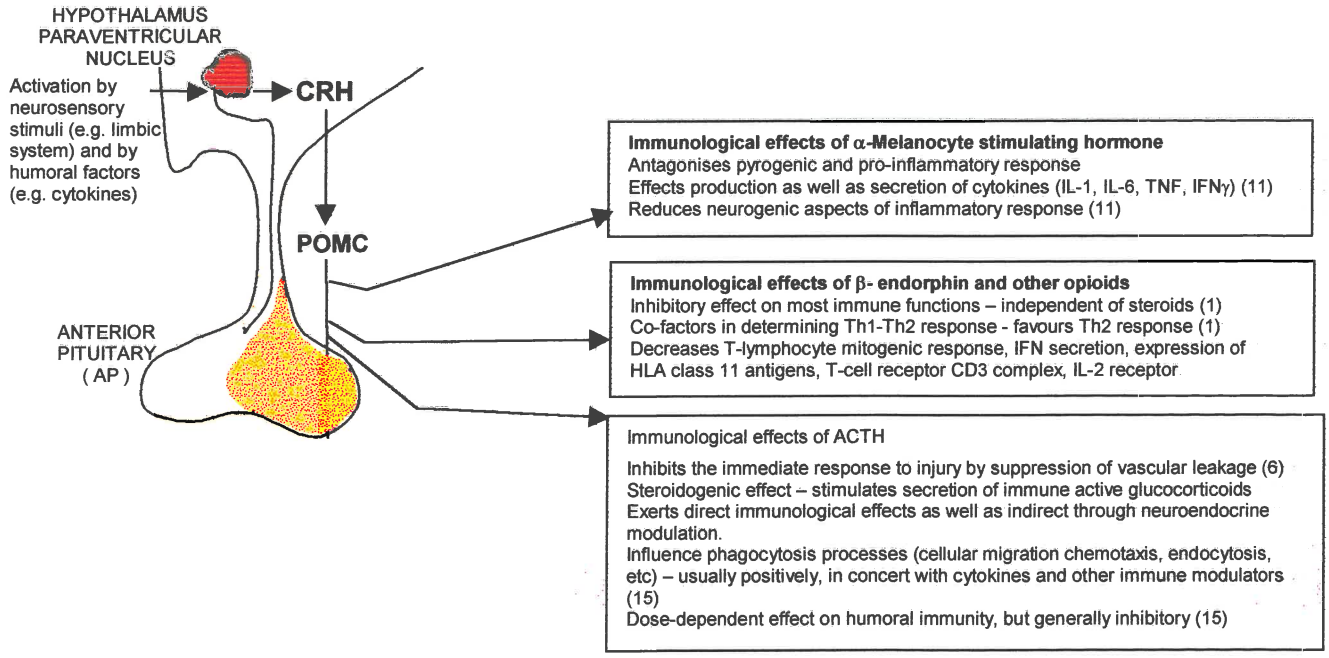

Figure 5.11: Immunological effects of other POMC-derived hormones of the HPA-axis

5.2.3 Corticotropin-releasing hormone (CRH) as direct immunoregulator

As already mentioned, CRH can influence the immune system through its regulatory influence on the HPA-axis, especially cortisol, as well as by controlling the total central neurohormonal stress response – including the CNA/SAM-axis. However, CRH has, in itself, immunoregulatory properties. These effects would in general appear to be pro-inflammatory. Nervous system derived CRH secretion is stimulated by stress-induced limbic system and other neurosecretory signals, and by humoral factors such as TNFα, IL-1 and IL-6. CRH can however, also be secreted by immunocompetent cells. Whether of neurosecretory origin or derived from immune cells involved in the inflammatory process, CRH can act as direct immunomodulatory autocrine or paracrine mediator of inflammation. It has, in fact been shown that immune cell hypersecretion of CRH may play a role in human autoimmune inflammatory diseases such as rheumatoid arthritis and

Hashimoto thyroiditis (77). These conditions of disturbed immunological homeostasis are known to be accompanied by behavioural alterations.

Some pro-inflammatory actions of CRH were shown in Figure 5.2 and for convenience sake reproduced below in Figure 5.12.

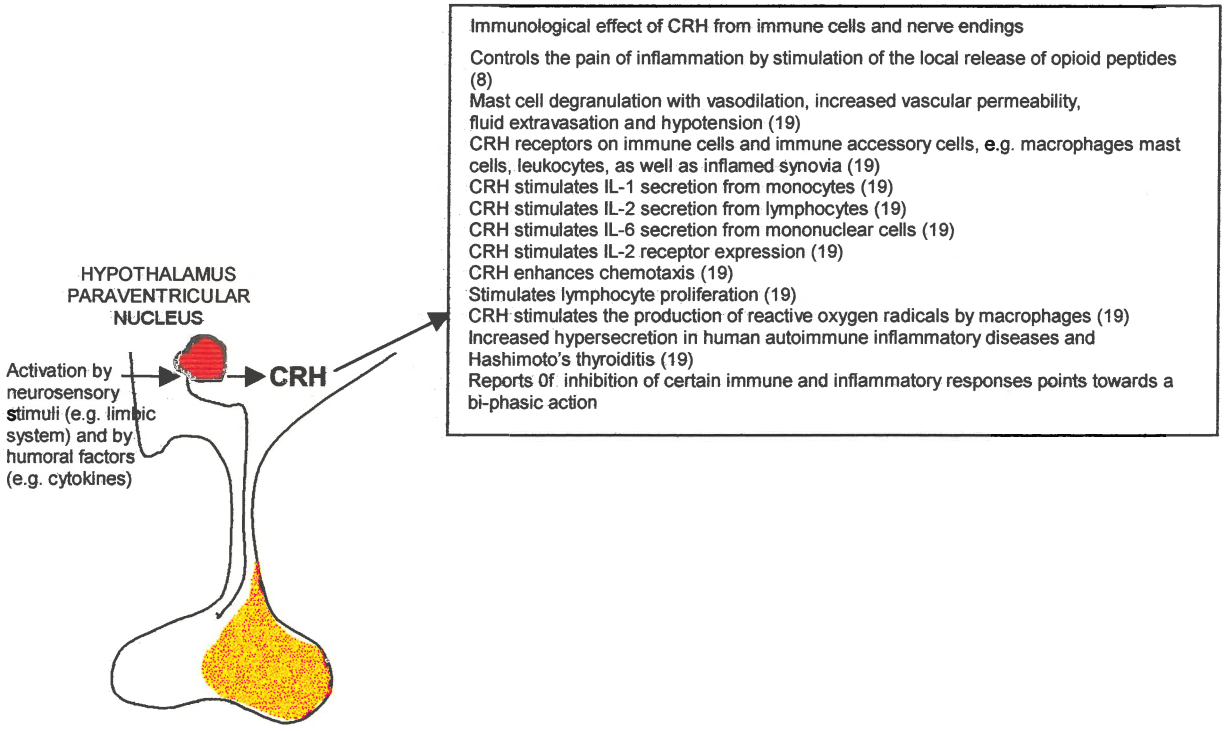

Figure 5.12: The pro-inflammatory effects of CRH

It is suggested that CRH, released from peripheral nerves, participate in an axon reflex loop with immune cells where the secreted CRH would stimulate the immune cells and immune accessory cells to initiate the immune response. This process has been implicated in stress-induced diseases such as asthma and eczema, as well as in the development of stress-induced migraine (77).

Immune cell-derived CRH is of importance in the initiation, propagation and regulation of inflammatory responses by enhancing pro-inflammatory actions such as vasodilation, increased vascular permeability, mast cell degranulation and increased chemotaxis, and by stimulating lymphocyte proliferation, pro-inflammatory cytokine secretion and

cytokine receptor expression (77). The paracrine pro-inflammatory actions of immune cell-derived CRH are mediated mainly through CRH-1 and CRH-2 receptors on neighbouring immune cells. A good review by De Souza is available on CRH receptors, their physiology, pharmacology, biochemistry and role in the immune system, as well as in the central nervous system (78). In view of the indications of a role for the inflammatory process in certain mental disorders referred to in Chapter 2, the wide distribution of CRH neurons within cerebral structures involved in the behavioural processes (referred to in section 1 of this chapter) and the pro-inflammatory role of CRH in immune regulation, it is tempting to speculate about a role for the CRH pro-inflammatory function in mental disturbances.

5.2.4 Indirect effects of CRH on immune regulation through its regulatory effects on neurohormonal substances which form part of the central stress response

As was be seen in the first section of this chapter, CRH is the main integrator and regulator of the stress response and, as such, exerts a major influence on the secretion of most neurohormonal substances. Most of these neurohormonal factors are able to influence the immune system and several of them are, in fact, also secreted by immunocompetent cells. Neurohormonal substances, involved in the stress response, of which the secretion are, to a greater or lesser degree, influenced by CRH, include noradrenaline, adrenaline, dopamine, serotonin, acetyl choline, histamine, thyroid hormones, growth hormone, prolactin, gonadotrophins and most other steroid hormones, endorphins, enkephalins, antidiuretic hormone, oxytocin, insulin, glucagon and a host other neurohormonal factors. All of these substances have immunomodulating functions – some immune-enhancing and other immunosuppressive – that act in concert to orchestrate the behavioural influences on immunity. The regulatory influence of CRH on these factors and their effects on the immune system will not be discussed here, but can freely be found in literature (61,79,80,81).

From a psychological point of view it is important to mention the stress spectrum hypothesis of Dhabhar and McEwen (82). The stress spectrum hypothesis states that one section of the stress spectrum is characterized by eustress, i.e., acute short duration stress

or controllable stress that would most probably result in immunopreparatory or immunoenhancing effects. This section of the stress spectrum is marked by a quick physiological stress system activation in the presence of the stressor, followed by a quick termination of the stress response once the stressor is removed. The opposite end of the stress spectrum is characterized by distress, i.e., chronic repeated or physiologically exhausting stress. This could very well be equated with uncontrollable stress and would generally lead to immune suppression. Distress is generally characterized by either persistence of the physiological stress response long after the stressor had been removed or by repeated activation of the stress response – sometimes without returning of the physiological mechanisms of the stress response to baseline values. This condition of repeated or continuous exposure to high activation of the physiological stress response, with its concomitant wear and tear on the psychophysiology, is often referred to as the allostatic load (83), and generally results in immune suppression. A third section of the stress spectrum, i.e., resilience, falls between the eustress and distress sections and is defined as the ability of the person to cope and survive for extended periods of time under conditions of increasing stress. This must surely be dependent on the coping skills of the individual and on his perception of controllability or uncontrollability of the situation. In this third section of the stress spectrum it is feasible to suspect immune function to be a product of the balance between all stress hormones – with CRH as main determinant.

Section 5.1 and Figure 5.1 demonstrated the distribution and central integrating role of CRH neurons and their projections in the nervous system. In section 5.2, Figure 5.2 and Figure 5.3, the central role of CRH in the neurohormonal control of the immune system was briefly illustrated. In these two sections it was seen that CRH performs a central role in psychoneuroimmunology in terms of the CRH/HPA-axis. Figure 5.4 (p5.11) presents an outline of this central role.

The next section will argue that *psychoneuroimmunology in terms of the two main stress axes* can, in fact, be translated into *psychoneuroimmunology in terms of CRH*.

5.3 Psychoneuroimmunology in terms of the two main stress axes.

5.3.1 The central role of corticotropin-releasing hormone.

This section, in integrating the information from sections one and two, argues that CRH does not only play a central role in the psychoneuroimmunological interactions of the CRH/HPA-axis, but also in that of the CNA/SAM-axis. The section therefore illustrates the central role of CRH in psychoneuroimmunology in terms of the two major stress axes. It requires very little explanatory text as the descriptions and references with regard to the CRH/HPA-axis were provided in the previous sections and that of the CNA/SAM-axis in Chapters 3 and 4. Figure 5.13 presents the concept in a simple diagram.

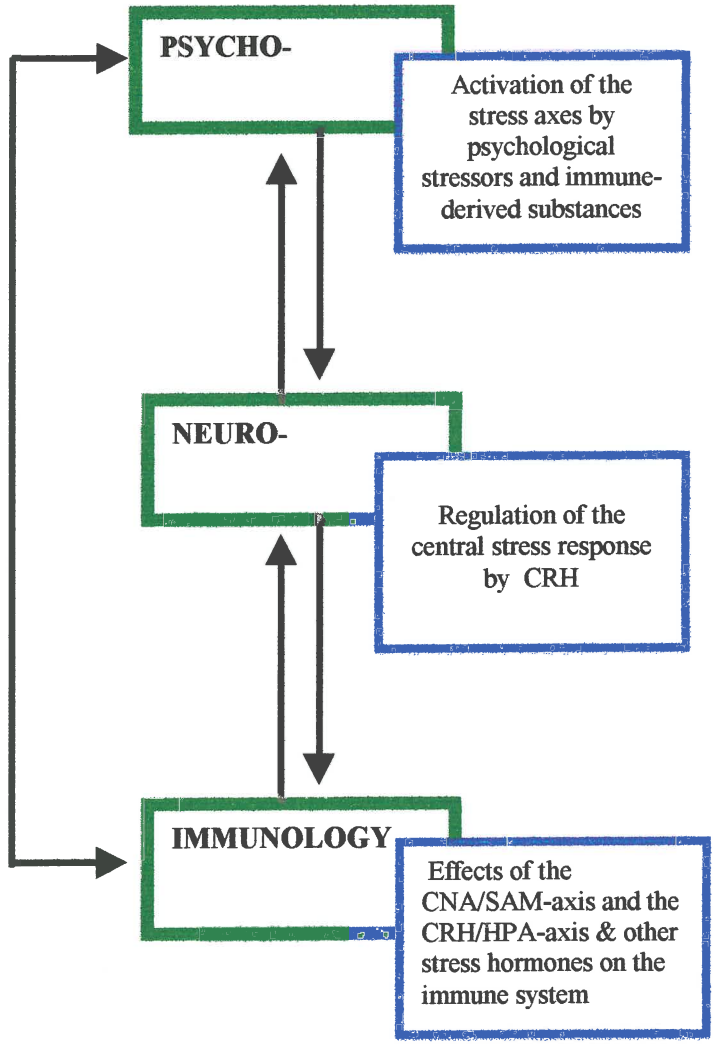

Figure 5.13 A heuristic diagram of psychoneuroimmunology in terms of the two main stress axes

An integrated full scale model with details CRH is presented as Figure 5.15 on page .

In order to see CRH as the central factor in the psychoneuroimmunological interactions of the two main stress axes it must be able to influence both the central nervous system (CNS) and peripheral functions of the two main stress axes. The question whether CRH can influence the central noradrenergic (CNA) system, or not, has already been answered in Chapter 3 where a reverberating positive feedback cycle was shown to operate between the CRH neurons and the (CNA) neurons. In addition, if CRH can influence the behavioural functions of the CNA system there should be some kind of correspondence between the behavioural effects of noradrenaline and CRH. The CNS noradrenergic functions and psychopathology associated with abnormal CNA activity were described in Chapter 3. Some of the functions and effects of the CRH system are touched upon in the next couple of paragraphs in order to show the correspondence.

5.3.2 Neurobehavioural effects of CRH

The neurobehavioural effects of CRH are summarized in Figure 5.14, and expanded on in

Behavioural functions and effects of CRH

- Most important is the regulation and integration of neuroendocrine, autonomic, immunological and behavioural aspects, especially during the stress response.
- As a result of the above, a regulatory function in almost all physiological and psychological processes.
- Acute, moderate increases in CRH generally leads to adaptational responses to stressors (increased alertness, controlled emotional and cognitive activation, decreased reflex time, moderare decreases in appetite and libido).
- Very high or chronic increases have negative physiological and psychological effects (anxiety and anxiety-related disorders, negative cognitive and emotional states, hyperresponsitivity to sensory stimuli, anorexia nervosa and sexual impotence).
- Pharmacological levels result in:
    - o Suppression of exploratory behaviour in strange environments
    - o Increased activity in familiar environment
    - o Decreased operant conflict reponses
    - o Changes in memory and learning
    - o Place and taste aversion
    - o Behavioural sensitization
    - o Enhanced stress-induced freezing
    - o Induction of seizures at very high levels
    - o Facilitation of acoustic startle
    - o Induction of conditioned fear
- Several mental disorders are known to be accompanied by high CRH (certain affective disorders, anorexia nervosa, obsessive-compulsive disorder, vulnerability to chronic drug abuse, the PMS syndrome), as well as by low CRH levels (seasonal depression, chronic fatigue syndrome, fibromyalgia, post traumatic stress syndrome).

Figure 5.14: The behavioural effects of central nervous system CRH

the pages to follow.

Corticotropin-releasing factor plays a role in a wide variety of behavioural and other functions, including sleep, arousal, motor function, feeding, reproduction, immunology, circadian rhythmicity, metabolism, as well as coping and learning behaviour (84,85,86). The CNA system was seen to be involved in all of the above (Chapter 3).

Stress-induced behavioural effects of CRH, as gleaned from the effects of the administration CRH agonists (87) further include

- Suppression of exploration of strange environments
- Increases in activity in familiar environments
- Decreased operant conflict responding
- Changes in learning and memory retrieval
- Place and taste aversion
- Behavioural sensitisation
- Enhanced stress-induced freezing
- Seizure inducement at very high dosages
- Facilitation of acoustic startle
- Induction of conditioned fear
- Suppressed sexual behaviour
- Suppressed feeding behaviour
- Increased grooming

Most of the above has been verified by attenuation of similar stress-induced behaviour by CRH antagonists. Many similar effects have been recorded with stress-induced increases in CNA/SAM-axis activity (Chapter 3).

It is important to remember that acute and moderate increases in CRH generally facilitate adaptation to adverse conditions, while chronic or very high acute levels of CRH have negative psychological, as well as physiological effects. Moderate increases in central nervous system CRH activity lead to increased alertness, controlled cognitive and

emotional activation, a decrease in reflex time, a moderate decrease in appetite and a decreased libido. However, with prolonged, high CRH activity the alertness will turn to anxiety and may even result in anxiety-related disorders, the cognitive and emotional activation turning into negative emotional states, the decreased reflex times being exacerbated to hyperresponsivity to sensory stimuli, the decreased appetite becoming anorexia nervosa and the suppressed libido sexual impotence (39,81). Similar biphasic effects are seen with activation of the central noradrenergic system (Chapter 3).

High CRH levels have been reported in several mental disorders including melancholic depression (88) anorexia nervosa (89), panic disorder, obsessive compulsive disorders, chronic alcoholism and alcohol withdrawal symptoms (90,91), exercise dependence, malnutrition and the PMS syndrome (39,81). It is also said to play a role in the vulnerability to addictions such as cocaine dependence (92). In contrast, subnormal levels are reported for conditions such as seasonal depression, chronic fatigue syndrome (93) posttraumatic stress syndrome and nicotine withdrawal (39,94). The mental disturbances associated with CNA abnormalities were recorded in Table 3.3 where high CNA activity was seen to be found in melancholic depression, eating disorders, obsessive-compulsive disorders, panic disorder, alcohol dependence, aggression, and others. Clear evidence exists that variations in basal CRH levels and CRH receptor density are associated with differences in stress adaptation (95). It is also clear that the stress pathology associated with either hyper- or hyposecretion of CRH can only be properly understood when the type of CRH receptor, the distribution as well as the density of these receptors are taken into consideration as receptor alterations are often the basis of changes in stress vulnerability and may predispose to mental disorders (95).

The most important function of CRH, and probably the one that forms the basis of most of its behavioural, as well as physical effects is the fact that CRH constitutes the principal neuropeptide in the regulation of the stress response (20,88). As can be seen in the middle section of the final integrated scheme at the end of the chapter (Figure 5.15), CRH neurons not only coordinate the central behavioural, but also the autonomic, endocrine, and motor function stress responses (84). It would, however, appear that different groups

of CRH neurons constitute the major mediators in the peripheral as opposed to the central behavioural stress response, with the PVN CRH neurons predominantly involved in controlling the peripheral, and the amygdalar CRH neurons in the behavioural responses. The amygdala is, however, important for the integration of these two modalities of the stress response as it sends information to both the brain stem and the hypothalamus. The brain stem, which receives processed information from the amygdala, also plays an important dual role as it is involved in the regulation of the peripheral SAM-axis, as well as in the regulation of the cerebral activation state and development of emotions by the brain. The CRH neurons of the brain stem are in a bidirectional communication with that of the amygdala and can in this way modulate the peripheral as well as behavioural stress effects. (20,31).The hypothalamus, in receiving information from the amygdala coordinates the autonomic and endocrine responses and by implication also the cortisol-associated behavioural functions. CRH, therefore, is indirectly in control of the behavioural effects of cortisol.

Most of the behavioural changes seen in association with abnormal CRH levels are mediated in conjunction with the effects of the central noradrenergic system, the glucocorticoids and the amygdala. However, CRH neurons in the hippocampus (explicit memory retrieval), the prefrontal cortex (important for fully formed concepts of awareness and elaboration of thoughts), as well as in other association and cortical areas, that help to do appraisals, to form perceptions and to weigh such perceptions up against sources of coping, are important for delivering pre-analysed, context-related information to the amygdala. The amygdala is known to a) receive information from virtually all neocortical sites (including highly processed information from the prefrontal cortex), b) to give meaning to processed information by analysing it against the backdrop of previous experiences, and c) to be the major structure involved in implicit memory. It is therefore an ideal structure for such involvement in the behavioural functions. As previously mentioned, the amygdala forms part of a network of brain nuclei interconnected by CRH neurons. The amygdala, being the origin of the major CRH projections throughout the emotional brain, sends CRH axons to the bed nucleus of the stria terminalis, the hypothalamus, the midbrain central grey, the autonomic nuclei of the

brain stem and to the aminergic nuclei of the brain stem – all structures intimately involved with behavioural and autonomic functions (20,31,54,87). A very important interaction between the CRH, the amygdala and the glucocorticoids is seen in the development of anticipatory anxiety (96). The amygdala is known to be involved in the anticipation of fearful and anxiety-producing events. It is, in fact, said that the activation of amygdaloid CRH mRNA by glucocorticoids may be responsible for the conditioned chronic expectation of negative events, and perhaps also in chronic arousal pathology (96). It has to be remembered that the amygdala, in contrast to the PVN, increases its CRH output when stimulated by cortisol (20). The implications of the development of anticipatory angst and chronic arousal in the young speaks for itself with regard to future adult mental and physical health. The importance of the CNA system in fear and anxiety-related disorders was dealt with in Table 3.2 and elsewhere in Chapter 3.

5.3.3 In conclusion

The ubiquitous distribution of CRH neurons and projections throughout the central nervous system enables the CRH system to influence and control a wide variety of functions. This makes it an ideal substance to be involved in psychoneuroimmunological integration. Its pervasive influence on the behavioural functions can probably be ascribed to the fact that CRH neurons and projections are present in all central nervous system areas involved in cognitive and emotive functions. In addition, CRH can directly as well as indirectly control immunological activity. Indirect effects include CRH's regulatory influence over other immunocompetent neurohormonal factors such as ACTH, β-endorphin, α-MSH, cortisol, as well as over hormones of the stress response. The fact that CRH from the paraventricular nucleus is in control of the HPA-axis is a well-known fact. However, CRH neurons from other brain centers such as the amygdala may also exert an influence on the HPA-axis. CRH would, however, also appear to be in control of the other stress axis, i.e., the CNA/SAM-axis. There can be no doubt that the CNA functions are strongly dependent on CRH activity. The most important pathway of the CRH control over central noradrenergic function is probably mediated via CRH projections from the central nucleus of the amygdala to the brain stem noradrenergic nuclei. With regard to the argument that the peripheral part of the CNA/SAM-axis, i.e.,

the sympathoadrenomedullary system is to a large extent under control of CRH, there can also be no doubt. In section two of this chapter it was shown that the activity of the SAM-axis is controlled by CRH neurons, not only at the level of the brain stem, but also at the level of the intermediolateral column of the spinal cord, the hypothalamus and the amygdala. (20,31). Some post-ganglionic sympathetic nervous system fibres have even been shown to be CRH-secreting fibres. The control of CRH over the SAM-axis was diagrammatically shown in Figure 5.1 and is incorporated into the final scheme of psychoneuroimmunology in terms of the major stress axes (Figure 5.15). In view of the central role of CRH in the control of the HPA-axis and in that of the CNA/SAM-axis it can by right be said that *psychoneuroimmunology in terms of the two major stress axes* can be equated with *psychoneuroimmunology in terms of CRH.*

In line with the title of the thesis the final full-scale version of *psychoneuroimmunology in terms of the two main stress axes* can be seen on the following page (Figure 5.15).

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ENVIRONMENTAL EVENT
APPRAISAL
Cognitively planned or conditioned
IGNORE
PERCEPTION
Non-threatening/ irrelevant
PRIMARY APPRAISALS
Believes & commitments
PERCEPTION
Threat or challenge
SECONDARY APPRAISALS
Resources, options, controllability
ACTIVATION OF CENTRAL STRESS RESPONSE
COPING BEHAVIOURS
Problem or emotion focused

PSYCHO -
Stress-induced CRH secretion

NEURO -
Neuronal-derived CRH
Integrates and coordinates
Autonomic, endocrine, motor, immunological, and behavioural responses

CRH NEURONS IN CENTRAL NUCLEUS OF THE AMYGDALA
HYPOTHALAMUS
INTEGRATION OF AUTONOMIC AND ENDOCRINE RESPONSES
Control of peripheral stress response
BRAIN STEM AUTONOMIC NUCLEI
CONTROL OF AUTONOMIC FUNCTION
CONTROL OF SAM-AXIS
Control autonomic stress response
BRAIN STEM AND AMINERGIC NUCLEI
Noradrenergic nuclei → cerebral activation
Cholinergic nuclei → learning & memory
Dopaminergic nuclei → alerting attention motivation
Serotonergic nuclei → excite cerebral neurons
Histaminergic nuclei → aggression diumal rhythm
Control central behavioural stress response
Integrated emotional and cognitive control

CRH NEURONS IN BRAINSTEM
N. Paragigantocellularis
Control of motor responses
+ SEROTONIN
- Acetyl choline
- β ENDORPHIN
- Dynorphin
- GABA
Control central behavioural stress response
Integrated emotional and cognitive control
Projection to brain stem N. tractus solitarius and to intermediolateral column of spinal cord
Locus coeruleus Noradrenaline (NA)
Control SAM-axis
Projections to CNS:
Cerebral activation
↑ NA: ↑ cerebral plasticity
(= behavioural adaptations)
↑↑↑ NA: cerebral damage & abnormal cognitive and emotional behaviour
Control cerntral activation

- IMMUNOLOGY
CRH effects
Pro-inflammatory response
CRH
Control of central stress response
Secretion of immunologically active stress hormones
NORADRENALINE
Necessary for immunocompetence
↑↑ levels: Immunosuppressive and anti-inflammatory
POMC
ACTH Immune effect
β-ENDORPHIN Immune effect
α-MSH Immune effect
ACTH
CORTISOL
Necessary for immunocompetence
↑↑ levels: Immunosuppressive and anti-inflammatory

CRH NEURONS IN HYPOTHALMUS (PVN) CRH
CNA-axis
Psychological stressor input from amydala
Cytokines
ANTERIOR PITUITARY
POMC
ACTH
β-ENDORPHIN
Stress buffer
β-endorphin Behavioural functions
INHIBITION
ADRENAL CORTEX CORTISOL
CORTISOL
Hippocampus Normal levels:negative feedback High levels: hippocampal damage and behavioural impairment
Hippocampus Diurnal rhyhms
Amygdala Stimulates CRH and ADH secretion by hypothalamus
Permissive actions Normal: metabolic regulation Abnormal levels: stress pathology
Control metabolic stress responses
Immunological effects Normal: immune enhancement Above normal: immune suppression
Control + integrate immune response
Behavioural effects of cortisol
- Stress adaptation - new homeostasis
- Warning signals of adversity
- Emotional and cognitive adaptational changes with chronic overproduction and chronic underproduction

Control behavioural adaptation

CRH NEURONS IN THE INTERMEDIOLATERAL COLUM OF THE SPINAL CORD
ACT ASPREGANGIOLIC FIBRES OF SYMPATHETIC SYSTEM
CONTROL AUTONOMIC STRESS RESPONSE

PREFRONTAL, INSULAR & CINGULATE CORTICES
CRH neurons help to integrate emotions into the CNS's formulation of the behavioural & physiological stress responses
Control and integrate working memory with rest of stress response

Figure 5.15 Psychoneuroimmunology in terms of the two main stress areas. The central role of corticotropin-releasing hormone.

Legend to Figure 5.15

Figure 5.15: Psychoneuroimmunology in terms of the two main stress axes. The central role of corticotropin-releasing hormone.

[The psychoneuroimmunological integration is shown in three layers with the top horisontal layer representing the *psycho-*, the middle layer the *neuro-* and the bottom layer the *immunological aspects*. This figure is a summary of the text and other figures of Chapter 5.]

This chapter dealt with the CRH/HPA-axis, firstly in terms of the psychoneurological interactions where the central nervous system CRH neuron distribution, the functions, and the interactions were illustrated, and secondly with the neuroimmunological interactions where the central role of CRH in neuroendocrine control of the immune system was demonstrated. The last section discussed the psychoneuroimmunological interaction in terms of the two major stress axes, i.e., the CRH/HPA-axis and the CNA/SAM-axis and showed that psychoneuroimmunology in terms of the major stress axes can translate into psychoneuroimmunology in terms of CRH. In order to understand the practical implications of psychoneuroimmunology it is necessary to know how immune-related events can influence behaviour. The next chapter will deal with the mechanisms through which the immune system can influence behaviour.

References

1. Panerai AE, Sacerdote P. β-Endorphin in the immune system: a role at last? Immunol Today 1997;18(7):317-319.

2. Wilckens T, DeRijk R. Glucocorticoids and immune function: unknown dimensions and new frontiers. Immunol Today 1997;18(9):418-422.

3. Didonata JA, Saatcioglu F, Karin M. Molecular mechanisms of immunosuppression and anti-inflammatory activities by glucocorticoids. Am J Resp Crit Care Med 1996;154:S11-S15.

4. Lim LHK, Solito E, Russo-Marie F, Flower RJ, Perretti M. Promoting detachment of neutrophils adherent to murine postcapillary venules to control inflammation: effect of lipocortin-1. Proc Natl Acad Sci USA 1998;95:14535-14539.

5. Wilckens T. Glucocorticoids and immune function: physiological relevance and pathogenic potential. TiPS 1995;16:193-197.

6. Thomas HA, Ling N, Wei ET. CRH and related peptides as anti-inflammatory agonists. Ann NY Acad Sci. :219-228.

7. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci 1998;94:557-572.

8. Schafer M, Mousa SA, Stein C. Corticotropin-releasing factor in antinociception and inflammation. Eur J Pharmacol 1997;323:1-10.

9. Perretti M. Lipocortin 1 and chemokine modulation of granulocyte and monocyte accumulation in experimental inflammation. Gen Pharmacol 1998;31(4):545-552.

10. Young JD, Lawrence AJ, MacLean AG, Leung BP, McInnes IB, Canas B, Pappin DJC, Stevenson RD. Thymosin-β-4-sulfoxide is an anti-inflammatory agent

generated by monocytes in the presence of glucocorticoids. Nature Med 1999;5(12):1424-1427.

11. Catania A, Lipton JM. The neuropeptide alpha-melanocyte-stimulating hormone: a key component of neuroimmunomodulation. Neuroimmunomodulation 1994;1:93-99.

12. Cidlowski JA, King KL, Evans-Storms RB, Montague JW, Bortner CD, Hughes Jr. FM. The biochemistry and molecular biology of glucocorticoid-induced apoptosis in the immune system. Rec Prog Horm Res 1996;51:457-491.

13. Angeli A, Masera RG, Sartori ML, Fortunati N, Racca S, Dovio A, Staurenghi A, Frairia R. Modulation by cytokines of glucocorticoid action. Ann NY Acad Sci 1999;876:210-220.

14. Kamm GL, Hagmeyer KO. Allergic-type reactions to corticosteroids. Ann Pharmacother 1999;33:451-459.

15. Ottaviani E, Franchini A, Genedani S. ACTH and its role in immune-neuroendocrine functions. A comparative study. Current Pharmaceutical Design. 1999;5:673-681.

16. Dhabhar FS, McEwen. Bidirectional effects of stress and glucocorticoid hormones on immune function: Possible explanations for paradoxical observations. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology. Vol 1, (ed 3). Academic Press, San Diego. 2001, pp301-328.

17. Issekutz TB, Effects of six different cytokines on lymphocyte adherence to microvascular endothelium and in vivo lymphocyte migration in the rat. J Immunol 1990;144:2140-2146.

18. The adrenal glands. In: RM Berne, MN Levay (eds). Physiology, (4th ed), Mosby, Inc., St Louis, Missouri, 1998, pp 945-948.

19. Elenkov IJ, Webster EL, Torpy DJ, Chrousos GP. Stress, corticotropin-releasing hormone, glucocorticoids and the immune/inflammatory response: acute and chronic effects. Ann NY Acad Sci 1999;876:1-13.

20. Central nervous system integration of the psychological stress response. In: WR Lovallo. Stress and Health. Biological and Psychological Interactions. Sage publications, Thousand Oaks, London, New Delhi. 1997, pp75-100.

21. Mastorakos G, Bamberger C, Chrousos GP. Neuroendocrine and endocrine regulation of the immune process. In: NP Plotnokoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Florida, 1999, pp17-38.

22. Selye H. The Stress of Life. New York: McGraw-Hill, 1956.

23. Sterling P, Eyer J. Biological basis of stress-related mortality. Soc Sci Med 1981;15E:3-42.

24. Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology. In: S Fisher, HS Reason, (eds). Handbook of life stress, cognition and health. New York, John Wiley and Sons, 1981.

25. Parrot WG, Schulkin J, Neuropsychology and the cognitive nature of the emotions. Cognitive Emotion 1993;1:43-59.

26. Mason J. Organisation of psychoendocrine mechanisms. Psychosom Med 1968;30:791-808.

27. Petrusz P, Merchenthaler I. The corticotropin-releasing factor system. In: CB Nemeroff (ed), Neuroendocrinology, CRC Press, Boca Raton, 1992, 129-183.

28. Davis M. The role of the amygdala in conditioned fear. In: JP Aggleton (ed), The amygdala: Neurobiological aspects of emotion, memory and mental dysfunction Wiley-Liss, New York, 1992, pp255-305.

29. Brown MR, Fisher LA, Spiess J, Rivier C, Rivier J, Vale W. Corticotropin-releasing factor: Actions on the sympathetic nervous system and metabolism. Endocrinology 1982;111:928-931.

30. Valentino RJ, Foote SL, Ashton-Jones G. Corticotropin-releasing factor activates noradrenergic neurons of the locus coeruleus. Brain Res 1983;270:363-367.

31. Lovallo WR, Thomas TL. Stress hormones in psychophysiological research. Emotional, behavioral and cognitive implications. In: JD Cacioppo, LG Tassinary, GG Berntson (eds), Handbook of Psychophysiology, 2nd ed, Cambridge University Press, Cambridge, 2000, 342-368.

32. Carpenter WT, Bunney WE. Behavior effects of cortisol in man. Sem Psychiatry 1971;3:421-434.

33. Jacobson L, Sapolski R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr Rev 1991;12:118-134.

34. Kovacs GL, Fekete M, Szabo G, Telegdy G. Action of ACTH-corticosteroid axis on the central nervous sytem. Front Horm Res 1987;15:79-127.

35. McEwen BS, Weiss JM, Schwartz LS. Selective retention of corticosterone by limbic structures in rat brain. Nature. 1968;220:911-912.

36. Wolkowitz OM, Reus VI, Weingartner H, Thompson K, Breier A, Doran A, Rubinow D, Pickar D. Cognitive effects of corticosteroids. Am J Psychiatry 1990;147:1297-1303.

37. Sapolski RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. Endocr Rev 1986;7:284-301.

38. Chrousos GP. Stressors, stress, and neuroendocrine integration of the adaptive stress response. The 1997 Hans Selye Memorial Lecture. Ann NY Acad Sci 1998;851:311-335.

39. Joël M, De Kloet ER, Effects of glucocorticoids and norepinephrine on the excitability in the hippocampus. Science 1989;245:1502-1505.

40. McEwen and Sapolski RM. Stress and cognitive function. Curr Op Neurobiol 1995;5:205-216.

41. McEwen. Atrophy of the human hippocampus. Psychiatry 1997;2:255-262.

42. Pavlides C, Watanabe Y, Magarinos AM, McEwen BS. Opposing role of Type I and Type II adrenal steroid receptors in hippocampal long-term potentiation. Neuroscience 1995;68:387-394.

43. Schulkin J. Corticotropin-releasing hormone signals adversity in both the placenta and the brain: regulation by glucocorticoids and allostatic overload. J Endocr 1999; 161(3):349-356.

44. DeLeon MJ, McRae T, Tsai J, George A, Marcus D, Freedman M, Wolf A, McEwen B. Abnormal cortisol response in Alzheimer's disease linked to hippocampal atrophy. Lancet 1988;2:391-392.

45. Meany MJ, O'Donnell D, Rowe W, Tannenbaum B, Steverman A, Walker M, Nair NP, Lupien S. Individual differences in hypothalamic-pituitary-adrenal activity in later life and hippocampal aging. Exp Gerontol 1995:30;229-251.

46. Rubinow D, Post R, Savard R, Gold P. Cortisol hypersecretion and cognitive impairment in depression. Arch Gen Psychiatry 1984; 41:279-283.

47. Starkman MN, Gebarski SS, Berent S, Schteingart DE. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. Biol Psychiatry 1992; 32:756-765.

48. Lupien S, Ngo T, Rainville C, Nair NPY, Hauger UL, Meany MJ. Spatial memory as measured by a human maze in aged subjects showing various patterns of cortisol secretion and memory function. Soc Neurosci Abst 1995; 2:1709.

49. Bremner JD, Randal P, Scott TM, Capelli S, Delaney R, McCarthy G, Charney DS. Deficits in short-term memory in adult survivors of childhood abuse. Psychiatry Res 1995;59:97-107.

50. al'Absi M, Hugdale K, Lovallo WR. Adrenocortical stress responses in relation to cognitive performance and hemisphere asymmetry. Psychophysiology 1998;35(suppl);S15.

51. Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer D. Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci 1996;58.

52. Curtis AL, Drolet G, Valentino RJ. Hemodynamic stress activates locus ceruleus neurons of unanesthetized rats. Brain Res Bull 1993;31:737-744.

53. Hilton SM. The defence-arousal system and its relevance for circulatory and respiratory control. J Exp Biol 1982;100:159-74.

54. Gray S. Amygdaloid CRF pathways. Role in autonomic, neuroendocrine, and behavioral responses to stress. Ann NY Acad Sci 1993;697:53-60.

55. Windhorst U. Bilateral organisation of the brain. In: Gregor R, Windhorst U, (eds). Comprehensive Human Physiology, Vol. 1, Springer-Verlag, Berlin, Heidelberg, New York, 1996, pp 1150-1154.

56. Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology 1998;23(3):219-243.

57. Francis DD, Caldji C, Champagne F, Plotsky PM, Meany MJ, The role of corticotropin-releasing factor-norepinephrine systems in mediating the effects of early experience on the development of behavioural and endocrine responses to stress. Biol Psychiatry 1999;46(9):1153-1166.

58. Radulovic J, Ruhman A, Liepold T, Spiess J. Modulation of learning and anxiety by corticotropin-releasing factor (CRF) and stress: differential roles of CRF receptors 1 and 2. J Neurosci 1999;19(12):5015-5025.

59. Gupta P, Brush FR. Differential behavioral and endocrinological effects of corticotropin-releasing hormone (CRH) in the syracuse high- and low avoidance rats. Hormones and Behavior 1998;34(3):262-267.

60. BJ Meyer. Die hipotalamus-hipofise-as: hipotalamus hormone.In: BJ Meyer *et al* (eds). Die Fisiologiese Basis van Geneeskunde (4th ed). Haum, Pretoria. 1988, pp57.1-57.12.

61. Cytokines. Stress and immunity. NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). CRC Press Washington DC, 1999.

62. How does the hormonal response induced by stress alter the immune system. In: BS Rabin. Stress, Immune Function and Health. The Connection. Wiley-Liss, New York, 1999, pp187-228.

63. Wilckens T. Glucocorticoids and immune function: Physiological relevance and pathogenic potential of hormonal dysfunction. Trends Pharmacol Sci 1995;16-193-197.

64. Wilckens T, DeRijk R. Glucocorticoids and immune function: Unknown dimensions and new frontiers. Immunol Today 1997;18:419-424.

65. Jeffries WM. Cortisol and immunity. Med Hypothesis 1991;34;198-208.

66. Dhabhar FS, Miller AH, McEwen BS, Spencer RL. Effects of stress on immune cell distribution – dynamics and hormonal mechanisms. J Immunol 1995;154:5511-5527.

67. Dhabhar FS, McEwen BS. Bidirectional effects of stress and glucocorticoid hormones on immune function: Possible explanations for paradoxical observations. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology. Vol 1, (3rd ed). Academic Press, San Diego, 2001, pp301-309.

68. Dhabkar FS, McEwen BS. Enhancing versus suppressive effects of stress hormones on skin immune function. Proceed Nat Acad Sci 1999;96:1059-1064.

69. Halliday WJ Garvey JS. Some factors affecting the secondary immune response in tissue cultures containing hydrocortisone. J Immunol 1964;93:757-762.

70. Thomason BT, Brantley PJ, Jones GN, Dyer HR, Morris JL. The relationship between stress and disease activity in rheumatoid arthritis. J Behav Med 1992;15:215-220.

71. Al'Abadie MS, Kent GG, Gawkrodger DJ. The relationship between stress and the onset and exacerbation of psoriasis and other skin conditions. Brit J Dermatol 1994;130:199-203.

72. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocrine Rev 1984;5:25-44.

73. Torpy DJ, Chrousos GP. The three-way interactions between the hypothalamic-pituitary-adrenal and gonadal axes and the immune system. Baillieres Clin Rheumatol 1996;10:181-198.

74. Black PH. Immune system-central nervous system interactions: Effect and immunomodulatory consequences of immune system mediators on the brain. Antimicrob Agents & Chemother 1994;38:7-12.

75. Zwilling B. Stress affects disease outcomes. Confronted with infectious disease agents, the nervous and immune systems interact in complex ways. ASM News 1992;58:23-25.

76. Irwin M. Stress-induced immune suppression: Role of brain corticotropin-releasing hormone and autonomic nervous system mechanisms. Adv Neuroimmunol 1994;4:29-47.

77. Elenkov IJ, Webster EL, Torpy DJ, and Chrousos GP. Stress, corticotropin-releasing hormone, glucocorticoids and the immune/inflammatory response: Acute and chronic effects. Ann NY Acad Sci 1999;876:1-13.

78. De Souza EB. Corticotropin-releasing factor receptors: Physiology, pharmacology, biochemistry, and role in central nervous system and immune disorders. Psychoneuroendocrinology 1995;20(8):789-819.

79. Stress and Immunity. N Plotnikoff, A Murgo, R Faith, J Wybran (eds). CRC Press, Florida, USA. 1991.

80. Kollack-Walker S, Day HEW, Akil H. Central stress neurocircuits. In: George Fink (ed), Encyclopedia of stress. Vol 3, Academic Press, San Diego, 2000, pp 414-422.

81. Chrousos GP. Stressors, stress and neuroendocrine integration of adaptive responses. Ann NY Acad Sci 1998;311-335.

82. Dhabhar FS, McEwen BS. Acute stress enhances while chronic stress suppresses immune function *in vivo*: A potential role for leucocyte trafficking. Brain Behav Immun 1997;11:286-306.

83. McEwen BS. Protective and damaging effects of stress mediators: Allostasis and allostatic load. New Eng J Med 1998;338:171-179.

84. Venihaki M, Majzoub JA. Animal models of CRH deficiency. Frontiers in Neuroendocrinology 1999;20:122-145.

85. Nishino S, Mignot E, Benson KL, Zarzone VP Jr.. Cerebrospinal fluid prostaglandins and corticotropin-releasing factor in schizophrenics and controls: relationship to sleep architecture. Psychiatry Res 1998;78(3):141-150.

86. Welberg LA, Seckl JR, Holmes MC. Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotropin-releasing hormone: possible implications for behaviour. Neuroscience 2001;104(1):71-79.

87. Heinrichs SC, Menzaghi F, Pich EM, Britton KT, Koob GF. The role of CRF in the behavioural aspects of stress. Ann NY Acad Sci 1995;771:92-104.

88. Mitchell AJ. The role of corticotropin-releasing factor in depressive illness: a critical review. Neurosci Biobehav Rev 1988(5):635-51.

89. Kave WH. Neuropeptide abnormalities in anorexia nervosa. Psychiatric Res 1996;62(1):65-74.

90. Sarnyai Z, Shaman Y, Heinrichs SC. The role of corticotropin-releasing factor in drug addiction. Pharmacol Rev 2001;53(2):209-43.

91. Hundt W, Zimmermann U, Pottig M, Spring K, Holsboer F. The combined dexamethasone-suppression/CRH stimulation test in alcoholics during and after acute withdrawal. Alcoholism: Clin Exp Res 2001;25(5):687-691.

92. Sarnvai Z. Neurobiology of stress and cocaine addiction, studies on corticotropin-releasing factor in rats, monkeys and humans. Ann NY Acad Sci 1998;851:371-387.

93. Bradley LA, McKendree-Smith NL, Alarcon GS. Pain complaints in patients with fibromyalgia versus chronic fatigue syndrome. Curr Rev Pain 2000;4(2):148-157.

94. Yehuda R. Biology of posttraumatic stress disorder. J Clin Psychiatry 2000;62(Suppl 17):41-46.

95. Coste SC, Murray SE, Stenzel-Poore MP. Animal models of CRH excess and CRH receptor deficiency display altered adaptations to stress. Peptides 2001;22:733-341.

96. Schulkin J, McEwen B, Gold PW. Allostasis, amygdala and anticipatory angst. Neurosci Biobehav Rev 1993;18(3):385-396.

CHAPTER 6

IMMUNOLOGICAL INFLUENCE ON THE NERVOUS SYSTEM AND BEHAVIOUR: THE CENTRAL ROLE OF CYTOKINES

In Chapter 2 numerous examples of the psychoimmunological interaction were presented without exploring the underlying mechanisms. Chapter 4 and the second section of Chapter 5 dealt with the mechanisms through which psychologically induced activation of the two major stress axes can influence the immune system. What remain to be discussed are the pathways and mechanisms through which immunological activity can influence the brain and behaviour. Chapter 6 a) deals with the pathways through which immunological activity can influence the neurobehavioural functions, b) shows that immune-derived cytokines can act as stressors and initiate the stress response, c) overviews the types of influences of cytokines on behaviour, d) supplies evidence that immunological activity may predispose to future behavioural abnormalities and, e) argues that the CRH/HPA system is a primary target of immunologically derived cytokines.

Introduction

In previous chapters we have seen how the immune system can be controlled by behaviour. This behavioural control of the immune system, be it through classical conditioning, psychological `stress, deliberate psychological intervention or the effect of environmental impact, was shown to be mediated through neuroendocrine pathways. The effects of the two major stress axes on the immune system were discussed and CRH was shown to play a central regulatory role. This chapter deals with the influence of the immune system on the brain and on behaviour. The purpose of this chapter is to demonstrate how the brain can, consciously or subconsciously, become aware of the activity of the immune system, as well as the subsequent effects of this communication on the neurobehavioural functions.

The immune system, in addition to its defense against infectious agents and its surveillance functions, is in the process of being perceived as yet another sensory organ, informing the brain about potential dangerous events such as infections. The organs traditionally seen as sensory organs generally inform the brain about peripheral occurrences through impulses send via neural pathways. Such information about potentially harmful situations usually results in the conscious perception of events. Identification of infectious conditions by the immune system differs from that of the other senses in that information seldom leads to direct conscious perception of the condition and that the information can be transferred to the brain by mechanisms other than direct neural pathways. The information about infectious complications is said to reach the brain via the production and circulatory transport of immune cell-derived cytokines that signals the brain about the immunological activities. This could then, in the acute situation, alter central nervous system neurohormonal secretory activities that could induce behavioural adaptations such as sickness behaviour and other mental and cognitive changes. It is further said that chronic overstimulation of the immune system, especially during neurological vulnerable periods, may lead to psychopathology. Cytokines have been established as the major immunobehavioural substances.

To establish whether the above described immunological influences on the brain, and thus on behaviour, are scientific facts or merely folklore, the following questions should be asked

- Does the neural system have the necessary receptors for cytokines in order to exert an effect on the functions of the brain, and by implication on behaviour?
- How do these peripherally produced cytokines reach the neural structures involved in higher brain functions and behaviour? It is known that most of these structures are situated inside the blood-brain barrier – an organ not generally permeable to most circulating substances.
- Can cytokines influence the neural structures by, for instance, acting as stressors that initiate a stress response similar to that caused by psychological stress? How would

this then interact with non-immunological-induced stress, including psychological activation of the neurohormonal stress reaction?

- If so, are the effects merely of a transient nature or can cytokines lead to more permanent structural and functional changes that will influence future behaviour and perhaps predispose to mental disorders?
- Are the proposed cerebral cytokine receptors merely influenced by peripheral immune cell-derived cytokines or does the brain have a cytokine network that partakes in normal cerebral homeostasis?
- Are scientifically verified examples available to support the functionality of a cytokine-brain interaction, and perhaps of adverse conditions that may result from such an interaction?
- The CRH/HPA-axis, and more specifically CRH, has previously been shown to be central to psychoneuroimmunology in terms of the two major stress axes. Is this system to any significant extent influenced by cytokines?
- By integrating the information gained from all the chapters this far – can the brain and behaviour, in psychoneuroimmunological context, be programmed to be more stress resistant?

The aim of this chapter is to briefly review the answers to these questions. In this way it is hoped to show how the immune system functions as sense organ, informing the brain about immunological events in order to procure relevant neural and behavioural adaptations. This represents part of the bidirectional communication where immune products signal the brain and the brain signalling immune function, and hence coordinate the host defense response with other aspects of the stress response.

6.1 Cytokine receptors on neural structures

For cytokines to act as immunological messengers to the brain, the brain must have the appropriate cytokine receptors. Cytokine receptors have been shown on many cerebral structures. An idea of the distribution of cytokine receptors can be obtained from Figure 6.1, as adapted from Haas and Schauenstein, 1997 (1). The illustration in Figure 6.1 is

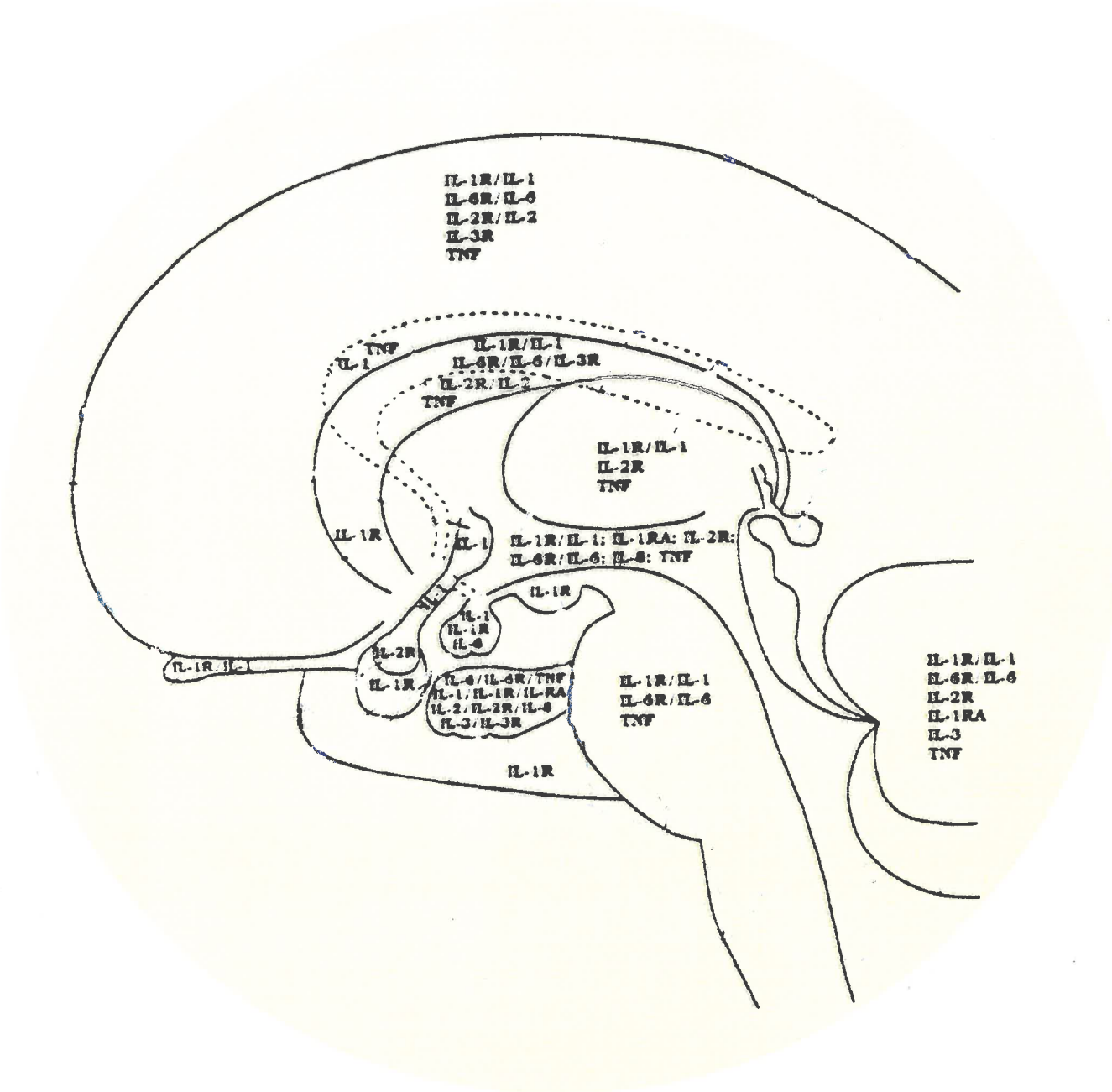

Figure 6.1: Cytokine receptors in the central nervous system
Adapted from (1)

still far from complete as new information is consistently being published. As would later be seen, stress hormones modulate the expression of some of the receptors. Apart from the expression of cytokine receptors in the brain, certain CNS cells can also produce cytokines, particularly microglial cells and astrocytes (2). The production of these cytokines can be constitutive or inducible – rendering their production open to psychoneuroimmunological modulation. Cerebral production of cytokines can be induced either by peripherally derived immune signals or by neuronal signals (3). More about cytokine production and function in the brain at a later stage of the chapter.

6.2 Pathways by which cytokines can influence the brain and behaviour

The presence of cytokine receptors in the brain offers the opportunity for immunological activity to influence the neurobehavioural functions – if the cytokines can get pass the blood-brain barrier. Various routes exist through which cytokines can influence neural function and it is postulated that different routes predominate under different conditions (3). Some of the pathways by which cytokines and other immunomodulators can influence the central noradrenergic system were referred to in Chapter 4 and would not be dealt with in this chapter.

Although we are primarily interested in the effects of peripherally derived cytokines on the brain and behaviour, it should be mentioned that immune-neural interactions also occur locally in peripheral areas. This is especially true with regard to the SAM-axis where locally produced IL-1 can control noradrenaline secretion from postganglionic sympathetic nerve fibres innervating primary and secondary lymphoid tissues (3). This local immune-neural interaction is referred to as the short-loop interaction between cytokines and neural elements. The second mode through which cytokines can influence neural tissue is by cerebral cytokines produced *in situ*, as previously mentioned (2,3). The third route involves the mechanisms through which peripherally produced, immune cell-derived, cytokines signal the central nervous system and behaviour.

Of all the cytokines, the way the interleukin-1 (IL-1) family of cytokines signals the brain is probably best understood. The reason why more work is done on IL-1 signalling is that we are for quite a while aware of the fact that IL-1β plays a role in fever-induction and that many workers were involved in finding the way in which IL-1 manages to reach the relevant neural structures. However, not one cytokine operates in isolation from other cytokines, they are all extremely pleotropic, and a great deal of functional and mechanistic overlap occur. The reason why the signalling of IL-1, and specifically IL-1β is of great importance for this writing is that it forms part of the non-specific or innate immune response. The cytokines of the IL-1 family are, in fact, members of the pro-inflammatory cascade of cytokines released by activated macrophages, that include, amongst others, IL-1α, IL-1β, TNFα and IL6. It is further known that IL-1β induces IL-2 production by T-helper (Th) cells, as well as the expression of IL-2 receptors (3,4). This becomes relevant when the effects of IL-2, a major immuno-neural communicator, are discussed in a later paragraph. The importance of the pathways for neural signalling via these pro-inflammatory cytokines turn out to be of even greater importance and relevance to the integration of the mind-body effects of cytokines when one recalls that (4) they

- Initiate and coordinate the inflammatory response – a response implicated in a number of mental disorders (refer to chapter 2).
- Initiate the acute phase response – a response that includes several adaptative mechanisms against injury and trauma, including physiological responses such as the hepatic shift to acute phase protein production, redistribution of iron stores and the induction of fever. These physiological alterations each have behavioural effects of their own. However, the acute phase response is also marked by a host of behavioural alterations grouped together under the rubric of "sickness behaviour". Sickness behaviour will be addressed in the next chapter as part of a model developed to illustrate the practical implications of the psychoneuroimmunological interaction.

The mechanisms of the third pathway through which cytokines signal the central nervous system and behaviour include blood-borne mechanisms where cytokines are transported

from the area of secretion to the brain, as well as neural mechanisms where cytokines influence peripheral nerves that in turn transfer the information to the cerebral structures.

Signalling through circulatory transport of cytokines, i.e., blood-borne mechanisms include

- Cytokine carrier mechanisms. Saturatable cytokine carrier-mediated mechanisms can transport cytokines across a concentration gradient to the brain and are responsible for at least a small part of the signalling process (4,5).
- Entry of cytokines at the circumventricular organs (CVOs) (4,6). These areas are devoid of a blood-brain barrier and include the area postrema (AP) and the organum vasculosum of the lamina terminalis (OVLT). Entry through these areas does, however, not provide entry to the rest of the brain, i.e., areas where the cytokine-behavioural interactions are known to take place. Cytokines bind to cytokines receptors on the CVOs – an event that stimulates prostaglandin synthesis. Prostaglandins, which are highly lipophilic and, in many instances, also neuroexcitatory, then cross the blood-brain barrier to cerebral areas not accessible to cytokines. Prostaglandins can now activate neurons that, in turn, project to appropriate areas such as the paraventricular nucleus and other structures of the HPA-axis, as well as to cerebral structures such as the amygdala and central noradrenergic neurons (6,7,8). The potential neuro-behavioural effects are self-evident.
- Binding of cytokines to cytokine receptors on cerebral blood vessels with subsequent signal transduction. The process is very similar to that of binding to receptors on the CVOs. Cytokine binding to these receptors on the vasculature can, as before, lead to prostaglandin synthesis through the COX-2 pathway, that will lead to neuronal activation and projection to the appropriate cerebral controlling areas – presumably with the same type of behavioural responses (4,9).

Signalling through effects on peripheral nerves occurs, amongst others, through vagal afferents. Immune cell-derived cytokines, such as IL-1, act locally, in a paracrine fashion, to stimulate vagal afferents that would then signal the appropriate cerebral areas. The

syndrome of behavioural characteristics known as sickness behaviour is but one of the patterns of behavioural adaptations to be initiated in this way (4). The transduction process probably involves cytokine receptors on paraganglia that surrounds vagal afferents. These paraganglia, which consist of chemosensory glomus cells, provide afferent innervations to vagal afferents by means of catecholamine and indolamine neurotransmission (10). The induction of prostaglandins may also be involved in the immune-neural signal transduction (1). In addition to the vagus nerve, other afferent nerves, including most cutaneous as well as the sciatic nerve, can also be instrumental in the immune-neuronal signalling process.

It would at present appear as if the early cerebral responses may be through prostaglandins formed via constitutive COX-2 upon vagus-induced noradrenergic input from the nucleus tractus solitarius (12), while blood-borne mechanisms come into play later, when cytokine levels have reached certain minimum levels (4).

6.3 Cytokine effects on neural structures and neurobehavioural functions – immunological activity as stressor

Immune cell-derived cytokines, although not the only substances, represent the major mediating vehicles for information transfer from the immune to the neurobehavioural system. In the previous section it was shown that signal transduction can occur either in the central nervous system or in the periphery. Evidence for the influence of immune-derived cytokines on the brain and on behaviour is provided in the next couple of paragraphs.

In previous chapters it was seen that the CNA/SAM-axis and CRH/HPA-axis, as well as other neurohormonal systems, form part of the response to psychological stress. It was also shown that the interactions between the two major stress axes and, especially, the neuromodulatory systems of the brain stem, including the serotonergic, GABA, dopaminergic and acetyl cholinergic systems, are major determinants of the cerebral activation state as well as mood. Further shown were the influences of the two major

stress axes on peripheral immunocompetence and cytokine production. As we have seen, stress-induced neurohormonal activation can influence cytokine production, as well as the clinical course of infections. The first question that should thus be asked is whether infectious conditions and subsequent cytokine release can, in turn, influence the neurohormonal activity and by implication behaviour. In other words, can such events initiate or alter the neurobehavioural stress response? The answer is an unequivocal yes. There is, in fact, a marked similarity between the infection-induced stress response and the psychologically-induced stress response. Activation of, not only the CRH/HPA-axis and CNA/SAM-axis, but also of most of the other neuromodulatory systems, takes place, both during psychological stress and infections (13,14). Examples of the stress-inducing effects of infectious events on the main stress-involved neural structures will be presented in the last section of this chapter. Infections can thus indeed be seen as stressors with the ability to initiate the central nervous system stress response. Minor differences exist between the response initiated by psychological stress and that caused by infection – the major differences apparently that the infectious complications generally initiate larger noradrenaline responses in the hypothalamus than in other brain areas and that the dopamine response is virtually absent (13,14). An almost identical induction of the central stress response has repeatedly been reported with endotoxin (lipopolysaccharide or LPS) administration. However, the neuroendocrine/neurochemical response of LPS has, as could be expected, a much more rapid onset (13,14). A great number of studies showed that cytokines could exert a similar stimulatory pattern on the central neuroendocrine stress response. The main cytokines involved in initiating the central stress response would appear to be a) interleukin-1α and interleukin-1β, which stimulate the 2 major stress axes, as well as the tryptophan and serotonin, but not the dopamine system, b) interleukin-2 which stimulates, at least, the same systems, c) interleukin-6 that stimulates, at least, the CRH/HPA-axis and central serotonergic system, and d) tumour necrosis factor-α that stimulates the two main stress systems (13,14). Detailed descriptions of the effects of the various cytokines on the different cerebral regions involved in the stress response are available (13), but beyond the scope of this thesis.

The previous paragraphs discussed the ability of cytokines to initiate, like any psychological stressor, the central nervous system stress response. It speaks for itself that in activating a neurohormonal activation similar to that of psychological stressors, cytokines would also be able to cause behavioural changes similar to that of psychological stress.

Of interest to note is the fact that the two main stress axes would appear to contain the release of those cytokines that are known to have the most significant influences on the neurobehavioural processes. This is at least true for noradrenaline and the glucocorticosteroid, cortisol. As previously shown, these stress hormones differentially influence cytokine production by T helper (Th) cells. Cytokine production by Th1 cells, i.e., the pro-inflammatory cytokines such as IL-2, IFNγ, TNFα and IL-12 are inhibited both by the effects of catecholamines on β2-receptors and by cortisol. Catecholamines and cortisol will, in certain conditions, stimulate the production of Th2 cytokines such as IL-4, IL-10 and IL-13, i.e., the anti-inflammatory cytokines (15). It would thus, at first glance, appear as if stress has only anti-inflammatory effects. However, it should be remembered, as shown in chapter 5, that the effects of other hormones such as CRH can be almost completely pro-inflammatory. Also of major importance, as mentioned in Chapter 4 and 5 with regard to the influence of the neurohormonal systems on the immune system, is the fact that the effects vary, depending on the duration of the stress, the type of stressor, the subject pool, the intensity of the stress response, i.e., the levels of neurohormonal activity, previous conditioning of animal or man, and many other factors.

In view of the differential effects of the two main stress axes on Th1 and Th2 cell-related cytokines it is not surprising to find that most of the cytokine effects, reported on the brain and on behaviour, are those of the Th1 cells – the cytokines most strongly controlled by the stress axes. The reader is referred to an excellent analysis by Hanisch, 2001 (16) on the cerebral effects, pathways, interactions, receptors and mechanisms of action of two classes of these cytokines, i.e., interleukin-2 and the interferon family. Numerous examples of neurological and behavioural effects of these cytokines are given and discussed by Hanisch (16), including

- Decreased food intake and eating behaviour (IFN)
- Altered motor activity (IFN)
- Induction of sleep (IFN)
- Decreased electrical activity of neurons, including putative CRH secreting cells in the paraventricular nucleus (INF)
- Modifications of EEG-like activity in somatosensory, motor and limbic structures
- Increased discharge of cortical and hippocampal neurons (IFN)
- Suppressed overall behavioural activity (IL-2)
- Decreased responding to rewarding lateral hypothalmic stimulation in rats (IL-2)
- Induction of asymmetric body posture and ipsilateral turning in rats (IL-2)
- Decreases or increases in hypothalamus neuronal activity – depending on the area of the hypothalamus (IL-2, IFN)
- Proconvulsive effects (IL-2)
- Suppression of afferent sensory transmission to neurons of the primary somatosensory cortex (Il-2)
- Increased ADH release from the hypothalamus and amygdala (IL-2)
- Inhibition of GH, FSH and LH release with increases in the release of somatostatin, prolactin and thyroid stimulating hormone (IL-2)
- Increases in cortisol levels (IL-2), POMC, ACTH and other POMC-derived hormones

Most of the cytokine effects shown above are similar to that expressed during the psychologically-induced stress response, as well as to symptoms found with a number of mental disorders. This supports the possibility that cytokines can act as neuroregulatory substances.

Typical examples of cytokine effects on the neurobehavioural functions will be discussed in more detail in a later section of this chapter. However, it is at this stage necessary to say that it is by now well established that cytokines can lead to a wide spectrum of neurobehavioural effects. The initial effects shown in animals have been supported in humans over and over again. Although it would be unethical to experimentally subject humans to the administration of relatively high dosages of cytokines, the opportunity to

study such effects became available with the introduction of cytokines and cytokine antagonists as therapeutic agents. At this stage it is believed that neurological and neuropsychiatric symptoms are common in at least 50% of patients treated with IL-2 or with interferons. The neuropsychiatric alterations include symptoms like cognitive impairments and cognitive failure, hallucinations, abnormal mood states, psychotic behaviour, headaches, motor weakness, confusion, somnolence, anxiety, paranoid delusions and combative behaviour. Reviews can be found on such mental changes (17). It should, however be stressed that the effects are not limited to brain and behaviour, but that a wide shift in total mind-body homeostasis occurs. These changes include further neurohormonally-induced alterations in the immunological activity (18).

6.4 Possibility that infections, with the accompanying changes in cytokine profiles, could cause long-term effects on the brain and perhaps predispose to future psychopathology

Another point of major interest is whether cytokines can modulate cerebral structure and hence have a more permanent effect on the brain and on behaviour. If this is possible it would give credence to claims that infectious complications, be it *in utero* or during early life, could predispose to behavioural problems in later life.

There are, in fact, ample indications to support the hypothesis that infectious complications can presensitise to future behavioural problems. Correlational studies between maternal immunological afflictions and behavioural problems, such as schizophrenia in the offspring, were already mentioned in Chapter 2. In addition, mechanisms through which such presensitisation processes may occur are slowly becoming clear. Research this far is focussed on the effects of cytokines. Interleukin-2 has, for instance, been shown to support survival and growth of a variety of neuronal and glial cells, but also, under certain conditions, to be toxic to neurons. A whole cascade of effects are reported for IFNα, IFNβ and IFNγ, including the prevention of cell death after cerebral injury by acting as nerve growth factor, a role in proliferation and scar-forming activities of glial cells, and neuronal cell death by direct, as well as indirect mechanisms

(19). The effects of glial scar formation on brain and behaviour are well known and would not be discussed at this stage. There is also sufficient evidence to believe that IFNγ can be instrumental in demyelinisation, be it through T-cell or other immune cell infiltration, or through the activity of resident glial cells (20,21). It is tempting to extrapolate this to the behavioural problems seen in demyelinisation disorders such as multiple sclerosis. Reported long-term effects of Il-2 therapy, including memory and neuroendocrine disturbances, delayed as well as progressive brain injury and permanent brain damage, further support the experimental evidence that cytokines can have long-term influences on neurobehavioural processes (16,17, 22,23). The implications of such damage to brain structure for future neurobehavioural abnormalities speak for themselves. This major route through which infections can presensitise neuro-endocrine systems to future psychological disorders is often overlooked.

It can at this stage unequivocally be stated that infectious complications can influence behaviour in the short-, as well as in the long-term. Firstly, it can act as stressor and elicit a stress response very similar to that of the psychological stress response. This was discussed in earlier paragraphs. In addition, the effects of the psychological stress response on brain structure and function can presensitise to the development of abnormal behaviour in later life. This aspect will be returned to in Chapter 7. In summary, one could conclude that exposure of the developing brain to infections, be it *in utero*, in early childhood, or even later, may have serious consequences for later mental health. In view of sustained cerebral plasticity through a large part of the life cycle this would probably also apply to infectious complications occurring during adolescent and adult life.

6.5 The cerebral cytokine network: The relay system hypothesis

As mentioned earlier in this chapter, the brain contains cytokine receptors, can synthesise cytokines - constitutive, as well as inducible – and cytokine production can be induced by immune as well as by neural signals (2,24). Some cytokines produced by the brain have been reviewed by Hori, Katafuchi and Oka, 2001 (25), and include

- Members of the IL-1 family, secreted in response to inflammatory, as well as non-inflammatory stress.
- Tumour necrosis factor alpha (TNFα), secreted under basal and stimulated conditions, with high levels in the hypothalamic area.
- Interleukin-6 (IL-6) and leukemia inhibiting factor, expressed during fever and LPS injection with significant concentrations in the hypothalamus and limbic structures.
- Interferon alpha (INFα), expressed constitutively, as well as induced during infections by neurons and glial cells, shown to be involved in the CNS-mediated acute phase response and, in contrast to most other pro-inflammatory cytokines, known to inhibit the HPA-axis.
- Interleukin-10 (IL-10), - a cytokine known to inhibit the production of pro-inflammatory cytokines, found in glial cells of humans and animals during infectious, traumatic, neoplastic and neurodegenerative diseases.

Others were shown in Figure 1 and mentioned elsewhere in the text. Although the discussion this far centered, but for IL-10, around the pro-inflammatory cytokines, anti-inflammatory cytokines such IL-4, IL-10, IL-13 and TGF-β can also be produced in the brain. It is at present safe to say that they can, in cooperation with substances like the glucocorticoids and antidiuretic hormone, oppose the expression and actions of pro-inflammatory cytokines in the brain, i.e., it can offer some protection against pro-inflammatory cytokine-induced behavioural effects such as depression (26).

The induction of cerebral cytokine production by peripheral immunological activity leads to differential cytokine expression in very specific cerebral areas, especially the hypothalamus, hippocampus and thalamus-striatum. The cytokines thus produced are then, in turn, able to exert a controlling influence on the local neurohormonal structures. One can assume the purpose of this cytokine-induced response to be the coordination of those peripheral homeostatic processes that are under cerebral control (24). In view of the overall coordination between physiological and psychological events shown in chapter 5, the process would most probably also coordinate behaviour with the physiological homeostatic adjustments.

Cerebral cytokine activity should, however, not be seen only as a phenomenon limited to periods of stress. The cerebral production of cytokines, induced by neuronal activity, forms part of normal cerebral function. A good example of the functionality of neuronal activity-induced cytokine production is the increase in IL-1β in the hippocampus during long-term potentiation (LTP) (27). LTP, part of the learning process and involved in memory formation, is marked by a sustained increase in synaptic transmission and post-synaptic neural activity. The cytokines produced in response to this increase in neuronal activity are, in turn, responsible for the maintenance of the LTP (24), and by implication necessary for normal learning and memory processes.

In view of the influence of peripheral cytokines on the immunological and neurological activities of the brain, a relay hypothesis, describing the dual immune and neural control of cerebral cytokine production, was proposed by Besedovsky and Del Rey, 2001 (24).

A relay system is postulated that integrates peripheral immune and neural/sensory signals, and induces a re-setting of neuro-endocrine functions. This relay system is based on interactions between cytokine-producing brain cells and neurons located in their close vicinity. When increased cytokine production is induced in areas such as the hypothalamus and the hippocampus as consequence of immune and/or neuronal signals, a resetting of homeostatic functions would occur (thermoregulation, glucose homeostasis, neuro-endocrine feed-back, etc). This resetting of homeostasis is expected to be specially relevant for neuro-endocrine adjustments needed during conditions in which primarily the immune system (e.g. infections) or the CNS (e.g. stress) is affected.

Besedovsky and Del Rey, 2001 (24).

Figure 6.2, based on the work presented in this chapter, including the relay hypothesis of Besedovsky and Del Rey, is a schematic representation of the psychoneuroimmunological interaction in which it is shown that

- The cerebral neuroendocrine systems responsible for behavioural characteristics can interact with the cerebral cytokine system under basal conditions. These interactions, as previously discussed, form part of normal processes such as learning and memory.

- During peripheral infectious or inflammatory conditions increased peripheral production of inflammatory cytokines will a) influence the cerebral neurohormonal systems and adaptive neurohormonal changes will occur, b) peripherally produced cytokines will induce increases in cerebral production of cytokines and c) inducible cerebral cytokine production will be further increased by the adaptational neuronal activity. In other words immune derived cytokines (non-cognitive stressors) signal neural structures via cytokine specific transport process, or via the induction of secondary signals such as prostaglandins through receptors on blood vessels or circumventricular organs, or through the influence of cytokines on peripheral afferent nerves. This signalling leads to adaptive changes in neurohormonal functioning which in themselves are stimuli for further cerebral induction of cytokine production. Cerebral cytokine expression is thus upgraded both through the effects of the peripherally derived cytokines on the glial, neuronal and other brain cells, and through the cytokine-induced altered neuronal activity.
- The upgraded cerebral cytokine expression, in cooperation with high levels of peripheral cytokines change the activity and most probably the set points of the central nervous system neurohormonal control systems to bring about adaptational changes which help to cope physically and mentally with the stressor. This fits in perfectly with the concept of the stress condition primarily intended as an adaptational state.
- This adaptational state involves physiological processes, such as altered neurohormonal functioning, that lead to adaptive behavioural processes, as well as adaptive metabolic, motor, sensory and immunological responses. These adaptive responses result in a new mind-body homeostasis that enables the individual to cope mentally and physically with, in this case, the non-cognitive stressor.

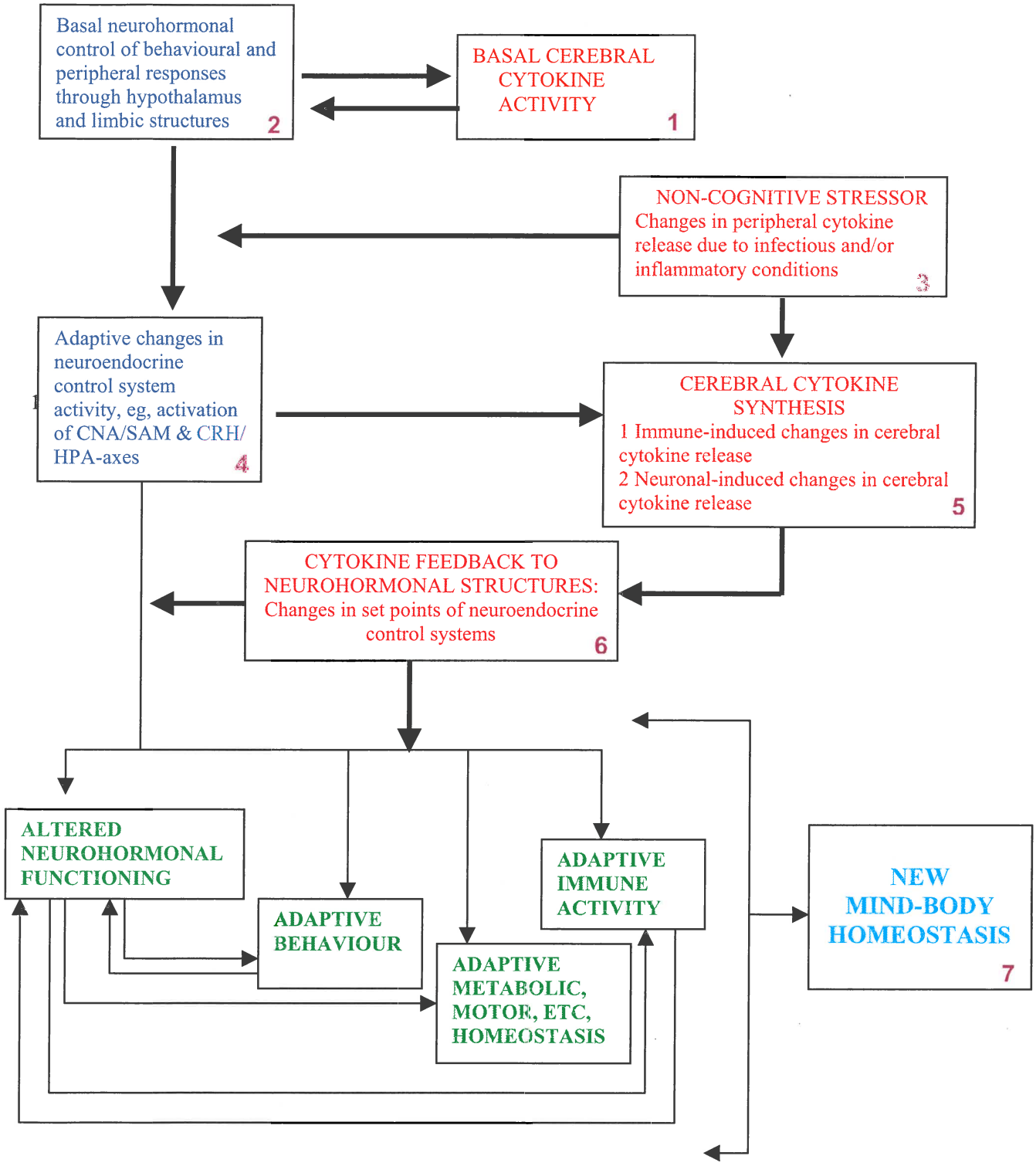

Figure 6.2: Relay hypothesis of the dual control of cerebral cytokine synthesis

[Figure 6.2 shows that basal cerebral cytokine production (1) plays a role in neuroendocrine activity (2) and *vice versa*. In the face of immunological activity, as non-cognitive stressor (3), selective neurohormonal activity (4) is increased by the effects of peripheral immune signals (cytokines) on the brain. Cerebral cytokine production is then increased by the effects of the peripherally-derived cytokines on the brain, as well as by the increased neurohormonal activity (5). This increased cerebral cytokine production can alter the neurohormonal set points (6) with subsequent development of a new mind-body homeostasis (7) characterized by alterations in behaviour and in the peripheral stress response]

The discussion above focussed on the changes that occur as a result of a non-cognitive stressor such as infection or a chronic inflammatory condition. This was intentionally done in order to show the psychoneuroimmunological interaction from an immunological point of intervention into the basic neuro-behavioural processes. This same schematic presentation will, however, apply should the primary stressor be of a psychological or environmental nature. The similarities between induction of the stress response by psychological and by immunological stressors were described earlier in this chapter.

What then is the relevance to the discussions on the CNA/SAM-axis and CRH/HPA-axis of previous chapters? This, based on discussions in previous chapters, speaks for itself, and has already been incorporated into Figure 6.2. The effects of the two major stress axes on peripheral immune responses are largely to curb excessive immune responses and have been discussed in Chapter 4 and Chapter 5 – before demonstrating that the central neurohormonal activity involved in the immunological control can actually be stimulated by the very same immunological activity. The neurohormonal activities of the two major stress axes are, in fact, amongst the most important neurohormonal immune regulatory mechanisms in the body. It is, as just mentioned, known that the cytokines centrally produced in response to peripheral immune activity also influence the two stress axes (28,29,30). This aspect will be further addressed in the last section of this chapter. It is thus possible for the immune system to, via the two main stress axes, indirectly feed back on its own activity and hence control its own activity in an integrated fashion with that of the neurohormonal and behavioural functions.

To summarise these effects of central cytokines, mediated via the related neurohormonal systems, on the peripheral immune response (25), it can be said that:

- Intracerebral IL-1β causes immune suppression through activation of the SAM-axis and HPA-axis (25,28,29,30).
- Cerebral IFN-α can suppress peripheral immunity through processes involving the sympathetic system, the opioids and CRH (25).

- IL-2 probably exerts its effects, if any, via activation of other hormonal responses (25).
- Opioids such as beta-endorphin, a component of the HPA-axis inducible by cerebral cytokines, probably cause immunosuppression in a process involving the SAM-axis (30,31).
- Corticotropin-releasing factor (CRH), as shown in Chapter 5, can be pro-inflammatory. However, it would appear to exert immunosuppressive effects through its control of the SAM-axis (25,28,32).
- Prostaglandin E_2 (PGE2), represents part of the pathway through which pro-inflammatory cytokines can induce the acute phase response. Here immune suppression would once again be dependent on activation of the two main stress axes (25,32) and thus on CRH activity.
- The cerebral cytokines may also be involved in the stress axes immunomodulation during non-inflammatory stress (see 25 for original references).
- Peripheral inflammation can also be controlled by cerebral cytokines. Peripheral inflammation can influence the CRH/HPA-axis through neural afferents or blood-borne cytokines and in turn be controlled by the axis (25,33). However, central pro-inflammatory cytokines may, under certain conditions, further enhance peripheral inflammatory conditions (34).
- Central cytokines can, in addition, modulate peripheral inflammation-associated nociception, with IL-1β, IL-6 and TNFα leading to hyperalgesia and IL-1α, IL-2, IFNα, TNFα contributing to analgesia. It would appear that cytokine-induced changes in CRH are involved, e.g., CRH can stimulate the local peripheral release of endorphins that will increase the pain threshold, while activation of the central noradrenergic and CRH systems may be involved in the central perception of the pain (25). The central cytokines may lead to hyperalgesia in the early phases of the disease, to act as warning system, and to sickness behaviour, an adaptational measure, in the more advanced stages.

It is perhaps, at this stage, necessary to return for a moment to the stress-induced neurohormonal effects of stress – be it psychologically-induced or immunologically-

induced. In previous chapters chronic stress was seen as predominantly immunosuppressive. Acute activation of the HPA-axis can, however, be immune enhancing (Chapter 5). Recently it was suggested that the psychological disposition before stressor application is a major determinant of the kind of immunological response elicited by psychological stressors. The work of Maes (18), showed that there are two kinds of stress-induced immunological profiles, i.e., a predominant suppressive immune regulatory response, and a predominant pro-inflammatory response. The pro-inflammatory response is associated with significant stress-induced anxiety and depression and the stress-induced cytokine production is sensitive to graded differences in the perception of stressor severity (18).

In this section it was shown that basal levels of cerebral cytokines are produced constitutively or are functionally induced. However, when peripheral immunological activity increases, the production of cerebral cytokines is upgraded. This increase in cerebral cytokine activity contributes to the integration of physiological and behavioural functions in a new adaptive homeostasis.

6.6 Practical examples of the immunological influence on neurobehavioural functions

Some examples were already given during discussions of the various mechanisms and pathways. This section will therefore present a wide overview of the effects the immune system exerts on the neurobehavioural functions in order to see the pervasiveness of the influence in perspective. Cytokines will again be shown to be the predominant primary mediators.

6.6.1 Cytokines, diseases of the central nervous system and psychiatric disorders

Cytokine involvement is known to contribute to the neurobehaviour abnormalities of CNS pathologies where inflammatory or autoimmune processes, or hyperactivation of glial cells are present. Examples include multiple sclerosis (MS), Alzheimer's disease (AD), stroke, post-traumatic lesions, as well as various other forms of neurodegeneration

and several psychiatric disorders (35,36,37). A good review of the role and mechanisms of cytokines in MS and AD, as well as the types of cytokines (IL-1β, TNFα, TFGβ, IL-6), the receptors and receptor complexes, the adhesion molecules, free radicals, and the redox sensitive transcription factors involved in CNS inflammation can be found in a writing by Merrill, 2001 (35). MS and AD are good examples of the influence of the inflammatory cytokines on behavioural functions in diseases of the adult central nervous system. In MS, an inflammatory, autoimmune, demyelinating disease, pro-inflammatory cytokine-induced damage to the myelin and myelin-producing oligodendrocytes lead to disturbed impulse conduction accompanied by abnormalities of motor and behavioural functions. AD, a neurodegenerative disease with marked cognitive and emotional changes, is now said to be primarily initiated by activated cytokine-producing microglia with subsequent inflammation and neuronal damage (35).

Abnormal cytokine production is further implicated in a large number of stress-related psychiatric disorders (38), including

- Obsessive-compulsive disorder (OCD). An increase in cytokine activity is reported in individuals with Sydenham's chorea, an infection-triggered autoimmune subtype of pediatric OCD and in Tourette's syndrome. The most prevalent cytokines in OCD would appear to be those associated with cell mediated immunity. (For further information on the immune activity in these two disorders, please return to Chapter 2.)
- Panic disorder where the most consistent cytokine deviation is a significantly higher IL-1β.
- Generalised anxiety disorder where the cytokine-related disturbances would appear to correlate with that seen in severe stress.
- Post-traumatic stress disorder where abnormal levels of IL-1β is once again reported as the most significant cytokine disturbance.
- Anorexia nervosa, a disorder generally associated with overactivity of the HPA-system, in which decreased IL-2 production and increases in IL-6 are reported.

- Many other stress-related psychiatric disorders in which the cytokine involvement where already referred to in Chapter 2.

The mood disorders are probably the psychiatric disorders best investigated in terms of immunological involvement, especially with regard to cytokines. There are some excellent overviews available on the immunological involvement in depression (39,40,41,42,43) and a short discussion here would be of little help. It is, however, necessary to mention that major depression is almost without exception accompanied by a moderate inflammatory response and by an increase in the secretion of pro-inflammatory cytokines. Depression and its associated cytokine profile would once again be returned to in the penultimate chapter of the thesis.

6.6.2 Neurobehavioural effects of cytokine therapy

A golden opportunity to study the effects of cytokines on human behaviour presented with the advent of cytokine therapy. Reported effects of cytokine therapy on the brain vary from mild headaches, to psychomotor retardation to psychiatric disorders to electroencephalographic changes – in a dose-dependent manner. In fact, two distinct patterns of cerebral toxicity are known to occur with cytokine therapy (44), i.e.,

- An acute phase where constitutional symptoms (fever, chills, headache and fatigue), now referred to as the flue-like syndrome, develop. It may last 1 to 3 weeks.
- A chronic phase, often referred to as neurasthenia or the chronic fatigue syndrome of cytokine therapy, with symptoms such as asthenia, malaise, lethargy, somnolence, headaches, low-grade fevers and anorexia. Other side effects such as psychomotor, cognitive and psychiatric abnormalities, including delirium and coma, may develop (44).

Typical neurobehavioural symptoms associated with specific cytokines, as summarised from an overview by Turowski and Triozzi, 1999 (44) include

- Interferon-α: At high dosages severe, chronic fatigue, psychomotor retardation, social withdrawal, gesticulation, articulation, anorexia and cognitive changes such as a decreased attention span, the inability to concentrate, suppressed verbal learning, impaired short term memory, loss of decisiveness and mental clouding, are common. Hallucinations, expressive dysphasia and gait difficulties may occur with chronic administration of high dosages. The psychiatric toxicities of interferon-α are sometimes classified into a) an organic personality syndrome (uncontrollable overreaction to minor frustrations, marked irritability, short temper), b) an organic affective syndrome (feelings of depression and hopelessness, tearfulness and crying), and c) a delirium category (clouding of consciousness, disorientation, the inability to perform simple calculations, memory problems, irritation and mood changes). The latter often not returning to normal after cessation of the treatment.
- Interferon-β: Symptoms are not as frequent and not as severe and, as before, depend on the dosage, administrative route and duration of therapy. Symptoms range from mild, acute constitutional symptoms, to chronic neurasthenia, to confusion, somnolence and emotional instability, to agitation, disorientation, dementia and personality changes.
- Interferon-γ: Symptoms, in a dose dependent fashion, range form mild constitutional problems such as headaches and chills and, infrequently, to dizziness, slowing of thought processes, confusion, crying episodes and Parkinson's-like symptoms – that are resolved upon cessation of therapy.
- IL-2: CNS toxicities occur frequently, ranging from constitutional problems to the less frequent appearance of somnolence, coma, disorientation and delirium at higher dosages during chronic administration.
- IL-4: Moderate grade fever, fatigue, anorexia, and headaches are common and there are indications that it may cause transient partial blindness, photophobia and visual hallucination at higher dosages.
- IL-12: Not properly investigated yet, but indications are that it causes fever, chills, headache and perhaps gastrointestinal and other problems.
- IL-1: This pro-inflammatory cytokine is at present not approved for clinical use due to its toxicity. Constitutional symptoms at low dosages with somnolence, confusion,

agitation, delusional ideation, photophobia, blurred vision and seizures at higher dosages are some of the symptoms reported when still approved.

- TNF: This is another pro-inflammatory cytokine at present not approved for clinical administration due to toxicity. Constitutional symptoms at low dosages, with amnesia, aphasia, hallucinations and diplopia at higher dosages were previously reported.
- IL-6: Yet another pro-inflammatory cytokine at present not approved for clinical use, despite reports that the toxicity is not as pronounced as that of IL-1 and TNF.
- Hematopoietins: Hematopoietins, including erythropoietin, granulocyte colony-stimulating factor, macrophage colony-stimulating factor, stem cell factor, interleukin-3, IL-11 and thrombopoietin all have a degree of neurotoxicity but are fairly well tolerated. Although the underlying mechanisms are said to be largely unknown, work in our laboratory showed that erythropoietin can dramatically increase intracellular calcium concentration – a cellular disturbance that is generally known to influence neuronal conductivity (45).

Cytokine therapy affects the behavioural functions through alteration of various cerebral activities. It can for instance

- induce secondary production of cytokines that can change the activity levels of specific neurohormonal circuits in the brain (46),
- alter the release of those stress hormones involved in cognitive function and emotion (47),
- alter behaviour through the development of auto-immune thyroid disease (48),
- change the circuitry of the frontal-subcortical circuit by influencing the neurotransmitters that control it (49) and
- influence the cerebral endothelium (47).

Many other examples of the influence of cytokines on the neurobehavioural functions are available, including fever, sleep and mood disturbances. However, a discussion on such aspects will be deferred to the next chapter where the cytokine-induced behavioural changes of sickness behaviour are to be discussed.

In line with the aim of this thesis it is, at this stage, necessary to show that the structures of the two main stress axes constitute major targets for cytokines.

6.7 The effects of cytokines on the CRH/HPA-axis – a regulatory role for CRH

In Chapter 5 the effects of the CRH/HPA-system on the immune system and cytokine production were described. The conclusion was that CRH is in fact the main neuroendocrine modulator of the immunological reactivity – be it direct or indirect. Chapter 5 further showed that CRH can coordinate all aspects of the psychological stress response, including the neurobehavioural, endocrine, autonomic and motor responses. It was, in fact, shown that "psychoneuroimmunology in terms of the two main stress axes" could perhaps be seen as "psychoneuroimmunology in terms of CRH".

In previous paragraphs of this chapter it was seen that the immune system has both short- and long-term effects on the brain and behaviour. To be able to equate "psychoneuroimmunology in terms of the two main stress axes" with "psychoneuroimmunology in terms of CRH" it is essential that one should be able to show that CRH neurons are major targets of the immune system derived cytokines. The next section will therefore deal, firstly with the effects of cytokines on the CRH/HPA axis, and secondly with that on the CRH system *per se*.

6.7.1 Effects of cytokines on the HPA-axis

The three parts of the HPA-axis that could theoretically be influenced by peripherally derived cytokines are the hypothalamus, the anterior pituitary and the adrenal cortex. Changes in the hormonal release from all three parts do indeed take place upon cytokine administration. An increase in CRH (and sometimes ADH) from the hypothalamus, ACTH from the anterior pituitary, and glucocorticosteroids from the adrenal cortex, have been shown in animals and in man upon administration of the IL-1 cytokine family (IL-1α, IL-1β), IL-2, IL-6, TNFα, IFNα and IFNγ. Indications are that some of the processes might be mediated through prostaglandin synthesis. The idea that cytokines can influence

the HPA-axis has over the last couple of years become an established fact (50,51,52,53,54,55,56,57,58,59,60), and would not be discussed in further detail.

6.7.2 Effects of cytokines on the corticotropin-releasing hormone (CRH) secreting neurons

The previous section showed the CRH/HPA-axis to be a major target of cytokines. However, there are strong indications that ACTH and glucocorticosteroids are released secondary to activation of the CRH and CRH/ADH neurons in the paraventricular nucleus (PVN) of the hypothalamus. In other words, that the PVN CRH neurons are the primary targets of the pro-inflammatory cytokines (61,62,63). Blockade of the CRH neurons with CRH-specific antibodies not only suppresses CRH secretion, in response to cytokine administration, but also the release of ACTH and glucocorticoids. It is also obvious that ADH, as in the case of the stress response to psychological stressors (Chapter 5), acts synergistically to enhance the effect of the cytokine-induced CRH on ACTH- and on subsequent cortisol-release. It is highly feasible to expect that ADH, as in the case of psychological stressors, will further augment the CRH effects on the behavioural functions. Depending on the route of administration the pro-inflammatory cytokines would appear to stimulate CRH secretion directly, or via prostaglandins and nitric oxide (NO) or carbon monoxide (CO) as secondary signals, or even via vagal afferents (62,63). Support for the earlier statement that the pro-inflammatory cytokines exert their cerebral functions largely by their actions on the CRH and CRH/ADH producing neurons of the paraventricular nucleus can be derived from research results which show

- That antibodies against CRH and ADH, as well as blockade of pituitary CRH receptors, prevent the HPA response to pro-inflammatory cytokines (64).
- The inability of TNF-α and IL-1β to stimulate the HPA-axis in PVN-lesioned rats (65).
- The PVN up-regulation of cNOS during endotoxaemia (66).
- Other similar experimental results as reviewed by Rivier, 2001 (61), as well as examples given earlier in this chapter.

Although the CRH neurons would appear to be the primary HPA-axis targets of peripherally derived cytokines, there can be no doubt that cytokines also do some fine-tuning of the system through an influence on other structures of the HPA-axis – and indirectly through effects on the noradrenergic neurons (61).

Directly relevant to the work discussed in chapter 5, and perhaps irrefutable support for CRH as major cytokine target, is the fact that a model has been developed - mapping the pathway of interleukin-2-induced release of CRH (67,68). The model involves muscarinic cholinergic receptors, nitric oxide (NO), cyclo-oxygenase activation, prostaglandin E synthesis, adenylate cyclase activation, cAMP generation and protein kinase A activation.

There seems, at least at this stage, to be very little difference between the final effect of cognitive and non-cognitive stressors such as cytokines on the hypothalamus. Other non-cognitive immune-related phenomena such as tissue injury (which, depending on the offending agent, may lead to preferential increases in some of the cytokines) and chronic inflammatory conditions such as arthritis, are also known to stimulate the PVN CRH neurons (61). In addition, some, at present considered non-immunological, non-cognitive stimuli such as haemorrhage (69), physical stressors such as restraint (70), as well as psychological stressors (71) have, however, also been shown to induce the production of pro-inflammatory cytokines. The role of cytokines in stress-induced stimulation of the PVN CRH neurons may thus be much more pervasive than suspected.

The PVN CRH neurons, as shown in Chapter 5, are the major regulators of the peripheral expression of the stress response. Also shown in Chapter 5 was the central role of the amygdalar CRH neurons in the behavioural aspects of the stress response. As in the case of the PVN CRH neurons, the amygdalar CRH neurons would appear to be important targets of cytokines with at least part of the cytokine-induced signalling of the amygdalar CRH neurons being NO-mediated (68). The importance of cytokine signalling of amygdalar activity can, with regard to the behavioural function, not be overestimated.

In view of the central role of CRH neurons as targets for pro-inflammatory cytokines, it can indeed be said that psychoneuroimmunology, in terms of the two major stress axes, can be equated with psychoneuroimmunology in terms of the CRH system with cytokines as a major interface between non-cognitive, and perhaps even cognitive stressors, and the neurobehavioural functions.

This chapter showed the pathways through which peripheral immunological events can influence neuroendocrine and behavioural functions and by acting as stressors, induce a new adaptive mind-body homeostasis intended to facilitate the necessary physical and psychological coping responses. Examples of the immunological influence on neurobehavioural functions were discussed, as well as the cytokine associations with a number of psychiatric disorders. The major neurobehavioural effects of cytokines were described and the CRH/HPA-axis, as well as CRH neurons of the amygdala, shown to be major targets of cytokine action. The next chapter will demonstrate the practical implications of the cytokine influence on the brain and behaviour.

References

1. Haas HS, Schauenstein KS. Neuroimmunomodulation via the limbic structures – the neuroanatomy of psychoimmunology. Prog Neurobiol 1997;51:195-222.

2. Fabry Z, Raine CS, Hart MN. Nervous tissue as an immune compartment: The dialect of the immune response in the CNS. Immunol Today 1994;15:218-224.

3. Besedovsky HO, del Rey A. Immune-neuroendocrine interactions: Facts and hypotheses. Endocrine Rev 1996;17:64-102.

4. Maier SF, Watkins LR, Nance DM. Multiple routes of action of interleukin-1 on the nervous system. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp563-583.

5. Banks WA, Ortiz L, Plotkin SR, Kastin AJ. Human IL-1 alpha, murine IL-1 alpha, and murine IL-1 beta are transported from blood to brain in the mouse by a shared saturable mechanism. J Pharmacol Exp Ther 1991;259:988-996.

6. Ericsson A, Arias C, Sawchencko PE. Evidence for an intramedullary prostaglandin-dependent mechanism in the activation of stress-related neuroendocrine circuitry by intravenous interleukin-1. J Neurosci 1997;17:7166-7179.

7. Lee HY, Whiteside MB, Herkenham M. Lesions of area postrema abolishes stimulatory effects of intravenous IL-1 on HPA activity and c-fos mRNA in the hypothalamic paraventricular nucleus. Brain Res Bull1998;46:495-503.

8. Ishizuka Y, Ishida Y, Kunitaki T, Kato K, Hanamori T, Mitsuyama Y, Kannan H. Effects of area postrema lesions and abdominal vagotomy on interleukin-1beta-induced norepinephrine release in the hypothalamic paraventricular nucleus region. Neurosci Letters 1997;223:57-60.

9. Cao C, Matsumura K, Yamagata K, Watanaba Y. Endothelial cells of the rat brain vasculature express cyclooxygenase-2 mRNA in response to systemic interleukin-1β: A possible site for prostaglandin synthesis responsible for fever. Brain Res 1996;73:263-272.

10. Ghoeler LE, Gaykema RPA, Nguyen KT, Lee JE, Tilders FJH, Maier SF, Watkins LR. Interleukin-1β in immune cells of the abdominal vagus nerve: An immune to nervous system link. J Neurosci 1999;19:2799-2806.

11. Ek M, Kurosawa M, Lundeberg T, Ericsson A. Activation of vagal afferents after intravenous injection of interleukin-1β: Role of endogenous prostaglandins. J Neurosci 1998;18:9471-9479.

12. Li HY, Ericsson A, Sawchenko PE, Distinct mechanisms underlie activation of hypothalamic neurosecretory neurons and their medullary catecholaminergic afferents in categorically different stress paradigms. Proc Nat Acad Sci 1998;93:2359-2364.

13. Dunn AJ, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. In: R Dantzer, EE Wolmann, R Yirmiya (eds). Cytokines, stress and depression. Advances in Experimental Medicine and Biology (vol 461). Kluwer Academic/Plenum Publishers, New York, 1999, pp117-127.

14. Dunn AJ. Effects of cytokines and infections on brain neurochemistry. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp649-666.

15. Hori T, Katafuchi T, Oka T. Central cytokines: Effects on peripheral immunity, inflammation and nociception. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp517-545.

16. Hanisch U-W. Effects of interleukin-2 and interferons on the nervous system. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp585-631.

17. Hanisch UK, Quirion R. Interleukin-2 as neuroregulatory cytokine. Brain Res Rev 1996;21:246-284.

18. Maes M, Song C, Lin A, De Jongh R, Van Gastel A, Kenis G, Bosmans E, De Meester I, Neels H, Janca A, Scharpe S, Smith RS. Immune and clinical correlates of psychological stress-induced production of interferon-γ and interleukin-10 in humans. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp59-73.

19. Vartanian T, Li Y, Zhoa M, Stefansson k. Interferon-gamma-induced oligodendrocyte cell death: implication for the pathogenesis of multiple sclerosis. Mol Med 1995;1:732-743.

20. Hartung HP, Schafer B, Van der Meide PH, Fierz W, Heiniger K, Toyka KV. The role of interferon-gamma in the pathogenesis of experimental autoimmune disease of the peripheral nervous system. Ann Neurol 1990;27:247-257.

21. Zhoa B, Schwartz JP, Involvement of cytokines in normal CNS development and neurological disease: Recent progress and perspectives. J Neurosci Res. 1998;52:7-16.

22. Hanisch UK Neuhaus J, Quirion R, Kettenmann H. Neurotoxicity induced by interleukin-2: Involvement in infiltration immune cells. Synapse 1996;24:104-114.

23. Hanisch UK, Neuhaus J, Rowe W, van Rossum D, Moller T, Kettenmann H, Quirion R. Neurotoxic sequences of central long-term administration of interleukin-2 in rats. Neuroscience 1997; 799-818.

24. Besedovsky HO, Del Rey A. Cytokines as mediators of central and peripheral immune-neuroendocrine interactions. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp1-17.

25. Hori T, Katafuchi T, Oka T. Central cytokines: Effects on peripheral immunity, inflammation and nociception. In R Ader, DL Felten, N Cohen (eds). Psycho-neuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp517-545.

26. Dantzer R, Bluthe RM, Castanon NC, Capuron L, Goodall G, Kelley KW, Konsman JP, Laye S, Parnet P, Pousset F. Cytokine effects on behaviour. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp719-722.

27. Schreier H, Pitossi f, Balschun D, Wagner A, del Rey A, Besedovsky HO. A neuromodulatory role of interleukin-1β in the hippocampus. Proc Nat Acad Sci USA 1998;95:7778-7783.

28. Hori T, Katafuchi T, Take S, Shimizu N, Niijima A. The autonomic nervous system as a communication channel between the brain and the immune system. Neuroimmunomodulation 1995;2:203-215.

29. Sunder SK, Cierpial MA, Kilts C, Ritchie JC, Weiss JM. Brain IL-1-induced immunosuppression occurs through activation of both pituitary adrenal axis and sympathetic nervous system by corticotropin-releasing factor. Neurosci 1990; 10:3701- 3706.

30. Take S, Mori T, Katafuchi T, Hori T. Central interferon-α inhibits natural killer cytotoxicity though sympathetic innervation. Am J Physiol 1993;265(2Pt2):R453-R459.

31. Hall DM, Suo JL, Weber RJ. Opioid mediated effects on the immune system: Sympathetic nervous system involvement. Neuroimmunology 1998; 83:29-35.

32. Katafuchi T, Ichijo T, Hori T. Sequential relationship between CRH and PGE_2 in the brain on splenic sympathetic nerve activity in rats. J Auto Nerv Syst 1997;67:200-206.

33. Turnbull AV, Rivier C. Corticotropin-releasing factor, vasopressin and prostaglandins mediate and nitric oxide restraints, the hypothalamic-pituitary-adrenal response to acute local inflammation in the rat. Endocrinology 1996;137:455-463.

34. Dulaney R, Macaluso A, Woerner J, Hiltz MA, Catania A, Lipton JM. Changes in peripheral inflammation induced by the central actions of an α-MSH analog and of endogenous pyrogen. Prog Neuroendocrinoimmunol 1992;5:179-186.

35. Merrill JE. Production and influence of inflammatory cytokines in diseases of the adult central nervous system. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp547-561.

36. Rothwell NJ, Relton. JK Involvement of cytokines in acute neurodegeneration in the CNS. Neurosci Biobeh Rev 1993;17:217-227.

37. Zhoa B, Schwartz JP, Involvement of cytokines in normal CNS development and neurological disease: Recent progress and perspectives. J Neurosci Res. 1998;52:7-16.

38. Weizman R, Bessler H. Cytokines: Stress and immunity – An overview. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp1-15.

39. Irwin M. Immune correlates of depression. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp1-24.

40. Maes M. Major depression and activation of the inflammatory response. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp25-45.

41. Seidel A, Rothermundt M, Rink L. Cytokine production in depressed patients. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp47-57.

42. Sluzewska A. Indicators of immune activation in depressed patients. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp59-73.

43. Leonard BE, Song C. Stress depression and the role of cytokines. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp251-266.

44. Turowski RC, Triozzi PL. Central nervous system toxicities and cytokine therapy. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp93-114.

45. Koorts AM, Kruger MC, Viljoen M. Intracellular calcium and transmembrane calcium fluxes in chronic renal failure patients. Clin Physiol & Func Im 2002;22:285- 294.

46. Licinio J, King MA, Hauser P, Cytokines and brain function: relevance to interferon-α-induced mood and cognitive changes. Sem Oncol 1998;25(suppl 1):30-38.

47. Meyers CA. Valentine AD. Neurological and psychiatric adverse effects of immunological therapy. CNS Drugs 1995;3:56-68.

48. Jones THJ, Wadler S, Hupart KH. Endocrine-mediated mechanisms of fatigue during treatment with interferon-α. Sem Oncol 1998;25(suppl 1):54-63.

49. Ho BT, Lu JG, Huo YY, Fan SH, Meyers CA, Tansey LW, Payne R, Levin VA. The opioid mechanism of interferon-α action. Anti-Cancer Drugs 1994;5:90-94.

50. Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 1987;238:522-524.

51. Denicoff KD, Durkin TM, Lotze MT. The neuroendocrine effects of interleukin-2 treatment. J Clin. Endocrinol 1989;69:402-410.

52. Naitoh Y, Fukata J, Tominaga T. Interleukin-6 stimulates the secretion of adrenocorticotropic hormone in conscious free-moving rats. Biochem Biophys Res Commun 1988;155:1459-1463.

53. Mastorakos G, Weber JS, Magiako MA, Gunn H, Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: Implications for the syndrome of inappropriate vasopressin secretion. 1994;79:934-943.

54. D'Urso R, Falaschi P, Canfalone G, Carusi E, Proietti A, Barnaba V, Balsano F. Neuroendocrine effects of recombinant α-interferon administration in humans. Prog Neuroendocrinoimmunol 1991;4:20-25.

55. Holsboer F, Stalla GK, Von Bardebelen U, Miler H, Miller OA, . Acute adrenocortical stimulation by recombinant γ-interferon in human controls. Life Sci 1988;42:1-5.

56. Sharp BM, Matta SG, Peerson PK, Newton R, Choa C, McCullen K. Tumor necrosis factor-α is a potent secretagogue: comparison to IL-1β. Endocrinology 1989;1989;124:3131-3133.

57. Tominga T, Fukata J, Naito Y. Prostaglandin-dependent in vitro stimulation of adrenocortical steroidogenesis by interleukins. Endocrinology 1991;128:526-531.

58. Andreis PG, Neri G, Nussdorfer GG. Corticotropin-releasing hormone (CRH) directly stimulates corticosterone secretion by the adrenal gland. Endocrinology 1991;128:1198-1201.

59. Falaschi P, Martocchia A, Proietti A, Pastore R, D'Urso R, Barnaba V. La Neuroendocrinoimmunologica. In: Atti dei Congressi della Societa Italiana di Medicina Interna. 94° Congresso, Edizioni L Pozzi, Roma, 1993, p315.

60. Falaschi P, Martocchia A, Proietti A, D'Urso R. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp325-327.

61. Rivier C, The hypothalamo-pituitary-adrenal axis response to immune signals. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp633-648.

62. Rivier C. Influence of immune signals on the hypothalamo-pituitary axis of the rodent. Front Neuroendocrinol 1995;16;151-182.

63. Watanobe H, Sasaki S, Takebe K. Evidence that intravenous administration of interleukin-1 stimulates corticotropin-releasing hormone secretion in the media eminence of freely moving rats: Estimation by push-pull perfusion. Neurosci Lett 1991;133:7-10.

64. Rivier C. Blockade of nitric oxide formation augments adrenocorticotropin release by blood-borne interleukin-1β: Role of vasopressin, prostaglandins, and α1-adrenergic receptors. Endocrinology 1995;136:3597-3603.

65. Kovacs KJ, Elenkov IJ. Differential dependence of ACTH secretion induced by various cytokines on the integrity of the paraventricular nucleus. 1995;7:15-23.

66. Lee S, Barbanel G, Rivier C. Systemic endotoxin increases steady state gene expression of hypothalamic nitric oxide synthase: Comparison with corticotropin-releasing factor and vasopressin gene transcripts. Brain Res 1995;705:136-148.

67.McCann SM, Karanth S, Kamat A, Les Dees W, Lyson K, Gimeno M, Rettori V. Induction by cytokines of the pattern of pituitary hormone secretion in infection Neuroimmunomodulation 1994;1:2-13.

68. Raber J, Koob GF, Bloom FE. Interleukin-2 (IL-2) induces corticotropin-releasing factor (CRF) release from the amygdala and involves a nitric oxide mediated signalling: comparison with the hypothalamic response. J Pharmacol Exp Ther 1995;272:815-824.

69. Komati G, Gottschall PE, Somogvari-Vigh A, Tatsuno I, Yatohgo T, Arimura A. Rapid increase in plasma IL-6 after hemorrhage, and posthemorrhagic reduction of the IL-6 response to LPS, in conscious rats: Interrelation with plasma corticosterone levels. Neuroimmunomodulation 1994;1:127-134.

70. Mekaouche M, Givalois L, Barbanel G, Siaud P, Maurel D, Malaval F, Bristow AF, Boissin J, Assenmacher I, Ixart G. Chronic restraint enhances interleukin-1-beta release in the basal state and after an endotoxin challenge, independently of adrenocorticotropin and corticosterone release. Neuroimmunomodulation 1994;1:292-299.

71. Maes M, Song C, Lin A, Jongh RD, Van Gastel A, Kenis G, Bosmans E, De Meester I, Benoy I, Neels H, Demedts P, Janca A, Scharpe S, Smith RS. The effects of psychological stress on humans: Increased production of proinflammatory cytokines and a Th-1like response in stress-induced anxiety. Cytokine 1998;10:313-318.

CHAPTER 7

A MODEL OF PSYCHONEUROIMMUNOLOGICAL INTERACTION

This chapter illustrates the practical implications of the psychoneuroimmunological (PNI) interactions presented in previous chapters. It therefore demonstrates the mind-body link in PNI context. A model of sickness behaviour in PNI context is presented as a condition of adaptational mind-body homeostasis and it is argued that abnormalities in the regulatory feedback processes could potentially lead to psychological and other disturbances. It is shown that experiences during early life could predispose to abnormal feedback mechanisms and thus to increased vulnerability to stress-induced mental and physical problems. The hypothesis is put forward that uncontrolled sickness behaviour may lead to any of a number of mental disturbances. Scientific evidence is provided in support of the hypothesis.

Introduction

The previous chapters dealt with evidence of the pervasive interaction between the immune system and the behavioural functions, as well as the mechanisms through which the various communications occur. In this, the final chapter, the practical implications of the psychoneuroimmunological interactions will be demonstrated. Sickness behaviour will be presented as heuristic model to show the important role of the psychoneuroimmunological influence on psychological health.. The potential danger of deviations in the regulatory feedback mechanisms, as well as the role of predisposition by early life experiences and negative emotions will be illustrated by presenting sickness behaviour in psychoneuroimmunological context.

Psychoneuroimmunology is a young discipline in which most of the empirical evidence was initially derived from the biomedical sciences. However, in the last couple of years an increase was seen in the output of psychoneuroimmunological studies from researchers in the humanities and from cooperation between the humanities and the

biomedical sciences. These interdisciplinary efforts between the humanities and the biomedial sciences helped to decipher underlying mechanisms of a number of psychological phenomena and to understand the practical implications of some of the neuroimmunological interactions. The majority of the psychoneuroimmunological studies that were performed primarily from the psychological perspective focused on the influence of negative emotions and events on health.

The concept that emotions can influence physical and mental health is generally well accepted by most disciplines. Indications from psychoneuroimmunological studies are that negative emotions such as depression, anxiety, hostility and anger may be among those posing the worst threats to health and that they may significantly increase morbidity and mortality rates (1). It is a well-established fact that negative emotions can also indirectly influence health by promoting unhealthy life styles that include drug abuse, and a decline in attention to nutrition, exercise, sleep requirements and hygiene (2). The effects of these indirect effects on health would appear to speak for themselves, but the underlying mechanisms for the direct effects are less clear. For many years the focus has primarily been on the neuroendocrine system in trying to explain the adverse effects of negative emotions on health. However, these neuroendocrine mechanisms could only account for a minority of the direct pathways through which negative emotions can influence health. Recently, through psychoimmunological investigations, it has become clear that stressors like negative emotions can lead to immune dysregulation and in this way have a negative influence on health. This can lead to persistent increases in peripheral pro-inflammatory cytokine levels with, as shown in the previous chapter, a positive feedback to cerebral cytokine production and sustained negative emotions (1,3). A vicious cycle indeed. In addition to the role of the immune system in the direct pathways, it has further become clear that immunological processes are also involved in the indirect effects of negative emotions on health and that the effects of sleep deprivation, malnutrition, drug abuse and other life style factors are often partially mediated through their effects on the immune system (2, & Chapter 1). Immune dysregulation is, in fact, not only involved in mediating the effects of these life style factors but could, as will be seen later in this chapter, be instrumental in contributing to

the abnormal sleep patterns, poor eating habits, drug abuse and other "unhealthy" behaviours which may result from negative emotions.

As in several other approaches to health or stress, psychoneuroimmunological investigations on the effects of negative emotions have been far more intensively researched than that on positive emotions. The following quotation is a good assessment of the situation

Although it is clear that negative emotions can intensify a wide variety of health threats, positive emotions have received considerably less attention, perhaps related to the prevailing view of physical and mental health as the absence of disease and negative emotions, as well as the fact that positive emotions are fewer in number and less differentiated than negative emotions. Indeed, although a substantial empirical literature exists for depression and objective measure of health, almost none exists for happiness and health, ----

Kiecolt-Glaser *et al*, 2002 (1)

The pathogenic potential of stressors, independent of whether the stressor is primarily mental or physical, is fairly unpredictable and no linear relationship can summarily be assumed between the type, or intensity, of the stressor and the outcome. The main determinants of the outcome would appear to be the presence of vulnerability and resilience factors, as well as predisposition to stress vulnerability. Psychoneuroimmnological studies to date have identified a number of vulnerability and resilient factors that can influence the outcome - partially by altering immune function. These factors, recently reviewed by Kiecolt-Glaser *et al*, 2002 (1,3), include sociodemographic variables (age, gender, socio-economic status, culture, ethnic identity and minority status), social relationships (personal relationships, social support), as well as personality traits and coping styles. These studies, in general, showed high vulnerability and low resilience often to be accompanied by increases in pro-inflammatory cytokine production – especially IL-6.

The other main determinant of stress outcome, as mentioned in the previous paragraph, is predisposition, either genetic or as a result of early life experiences. The predisposition-stress model (4) explains why only some individuals develop psychopathology in reaction to stressors and why those who do develop psychopathology can develop different disorders in response to the same stressor. It distinguishes between *necessary* conditions, such as predispositioning by previous life experiences and genetics without which psychopatholgy cannot develop, and *sufficient* conditions, i.e., the interactive and cumulative effects of predispositioning and stressors, that will inevitably lead to the development of psychopathology (4).

It is thus fairly indisputable that negative emotions can influence mental as well as physical health and that the immune system forms part of the pathways involved. The question remains whether, and if so how, disturbances in health can lead to negative emotions and behavioural dysfunction. Behavioural reactions like reactive depression or anger in the face of pain or disability are well known and do not warrant any further discussion. It is, however, also becoming clear that infectious conditions can lead to behavioural changes through cerebral cytokine-induced alterations in neurohormonal activity. The underlying mechanisms of cytokines on the behavioural functions were discussed in Chapter 6.

In the remainder of this chapter sickness behaviour, not to be confused with illness behaviour, will be discussed as a condition where negative emotions, other than reactive in origin, can develop as a result of physical illness. It will be seen that the illness does not necessarily need to be primarily infection-related and that sickness behaviour can, in fact, also result from psychological stress. Cross-sensitisation between psychological and physical stressors will be shown to exacerbate the behavioural symptoms. A hypothesis, postulating that the neurobehavioural symptoms of sickness behaviour can, depending on predispositioning, become mental disturbances, will be presented and defended. In this presentation the disease process will be seen as the precipitating stressor and sickness behaviour as the adaptive homeostasis.

The layout of this chapter comprises

7.1 Sickness behaviour as model of the psychoneuroimmunological interaction

- 7.1.1 Behavioural symptoms of sickness behaviour
- 7.1.2 Underlying mechanisms of sickness behaviour
- 7.1.3 The value of sickness behaviour as state of adaptation
- 7.1.4 Control of sickness behaviour

7.2 The influence of early life experience – predisposition or stress resistance

- 7.2.1 The effects of early life experiences on the neuroendocrine systems involved in behaviour
- 7.2.2 The effects of early life experiences on the immune system
- 7.2.3 Mechanisms underlying the predisposition to stress hyperresponsiveness, hyporesponsiveness and stress resistance

7.3 Termination of the symptoms of sickness behaviour and failure to terminate the response

7.4 The Hypothesis: Uncontrolled sickness behaviour may lead to any of a number of mental disturbances – partially dependent on predisposition by early life experiences

- 7.4.1 Mental disorders as a continuation of sickness behaviour

7.5 Summary

7.1 Sickness behaviour as a model of the psychoneuroimmunological interaction

7.1.1 Behavioural symptoms of sickness behaviour

Sickness behaviour is generally defined as the coordinated set of behavioural changes that develop during infection. However, as will be discussed later in this chapter, sickness behaviour can also be initiated by other factors and conditions. The symptoms of sickness behaviour include disinterest in the physical and/or social environment (often transiently accompanied by a lethargic, depressive mood, anhedonia and sometimes irritability), decreased locomotor activity, loss of reproductive drive, a decrease in body-care activities, fever, sleepiness and a loss of appetite - despite increased metabolic needs for the fever response (5,6). What is seldom recorded and yet experienced by many who suffered prolonged periods of illness is that behavioural symptoms such as feelings of worthlessness, guilt, nihilism and even suicidal contemplations may occur. It is perhaps of interest to quote Charlton, 2000 (7) when he wrote

The state of malaise, which prevails in sickness behaviour interacts with memories of the past and anticipations of the future such that a demotivated exhausted and profoundly dysphoric state of malaise fills and colors past, present, and the anticipations of future mental life. Prolonged sickness behavior therefore creates a nihilistic mental state where life seems devoid of gratifying possibilities (i.e. pessimism) because feedback to the brain registers a physiological state (i.e. emotion) that is locked into sickness behavior, and unresponsiveness to the usual appetites (i.e. anhedonia). Another factor is that the sufferers from sickness behavior does not know that they are sick, and often interpret their lack of energy, lack of motivation and poor concentration as a moral failure – leading to feelings of guilt and unworthiness. Charlton, 2000 (7).

There may be much to criticise in the above description, especially the assumption that the emotional components are described as locked into sickness behaviour. This, as we are by now fully aware of the fact that the behavioural aspects constitute a major part of sickness behaviour. The description of Charlton does, however, verbalise those aspects of sickness behaviour that are hardly ever expressed in writing.

Despite the bleak picture painted above, sickness behaviour is, in fact, not primarily a sickness-induced weakness and debilitation, but intended as a new mind-body homeostasis meant to enable the individual to best counteract the infection or whatever other stressor initiated the process. Sickness behaviour has very eloquently been described as a central motivational state with selection of the appropriate strategy in response to the eliciting disease, in other words, a reorganisation of behavioural and other coping activities (5,6). There is ample evidence to show that, if any other factor is perceived to threaten the survival and wellbeing of the individual more than the infectious complication, it would override the sickness behaviour, e.g., the fear motivational state may take precedence over the sickness motivational state (5,8,9), and behaviour would be aimed at counteracting whatever elicited the fear. Sickness behaviour can thus be seen as a state of adaptive perceptions and reorganisation of coping responses. It therefore speaks for itself that the CNS must be signalled as to the severity of the peripheral infection or inflammatory activity and that sickness behaviour must be controlled from within the central nervous system.

The signalling process from the periphery to the brain occurs via the induction of cerebral cytokine production by inflammatory cytokines released in response to peripheral infectious or inflammatory conditions, while the brain signals and controls the sickness behaviour through neurohormonal mechanisms. The following short description briefly deals with the adaptational value of sickness behaviour, and the underlying processes.

7.1.2 Underlying mechanisms of sickness behaviour

Sickness behaviour is initiated by pro-inflammatory cytokines produced by activated monocytes and macrophages in response to infections. In addition, gram-negative bacteria-derived lipopolysaccharides (LPS) can also stimulate the process by binding to the CD14 receptor on these mononuclear phagocytes. The major pro-inflammatory cytokines involved in sickness behaviour are IL-1, IL-6 and TNFα (10), with IL-1 seen as the prototypical pro-inflammatory cytokine (11). T cell-derived IL-2, in addition to the pro-inflammatory cytokines from mononuclear cells, may also contribute to the symptoms of sickness behaviour. The role of the IL-1 family, i.e., IL-α, IL-1β, the

receptor antagonist cytokine IL-1ra, and the receptors involved in sickness behaviour is rather complicated and is not discussed in detail. Suffice to say that IL-1β is produced as precursor, that several factors are involved in controlling the conversion to the active cytokine and in controlling IL-1 activity at receptor level. At receptor level the actions of IL-1 are, for instance, regulated by the type I IL-1 receptor which, via nuclear transcription factor NFκB, functions as the signal transducer, while type II IL-1 receptor down-regulates IL-1 actions by acting as decoy receptor in binding excess IL-1. Receptor activation can further be downregulated by the receptor antagonist cytokine IL-lra, which prevents signal transduction (12).

Cytokines, produced by peripheral immune cells, can signal the brain to up-regulate cerebral cytokine synthesis and release. The way the signal reaches the brain targets and the subsequent signal transduction were discussed in the previous chapter.

The intracerebral effects of pro-inflammatory cytokines can directly as well as indirectly cause all symptoms of sickness behaviour. The direct mechanisms involve alteration of the basal activity of neurohormonal systems like the hypothalamo-pituitary-adrenocortical axis, the central noradrenergic system and the central serotonergic systems (13). Cytokines may in addition act in synergism with the HPA-axis to change tryptophan, and by implication, serotonin (5-HT) metabolism. Tryptophan in being transported from the circulation to the brain is converted to 5-hydroxytryptophan and then to serotonin. However, immunological factors may stimulate the enzyme indoleamine 2,3-dioxygenase and glucocorticoids may stimulate the enzyme tryptophan 2,3-dioxygenase which will switch tryptophan metabolism away from serotonin in favour of the production of kynurenine with a subsequent decrease in tryptophan availability for serotonin synthesis (14). Indirect mechanisms involve activation of intermediates such as prostaglandin synthesis and nitric oxide (NO) release through intracerebral cytokine-induced COX-2 and inducible nitric oxide synthase (iNOS) activation. These intermediates are implicated in the alteration of neural pathways involved in several symptoms of the sickness behaviour, including somnolence, fever, as well as those physiological and behavioural symptoms mediated through activation of the central CRH

system and HPA-axis (5,15,16,17). For more detail on the contribution of specific cytokines on individual components of sickness behaviour the reader is referred to an overview by Dantzer *et al,* 1999 (18).

7.1.3 The value of sickness behaviour as state of adaptation

The value of fever during infection is still strongly debated. However, several arguments favour fever as an essential component of the host response to infection, including a) the argument that it is unlikely that a process as costly, in terms of energy expenditure, would have persisted throughout evolution if it did not have a function, b) the results of many studies which show that fever during bacterial infections is associated with a better prognosis, c) the increase in morbidity and mortality in animal studies on the use of antipyretics to attenuate fever, d) experimental evidence from hyperthermia and hypothermia studies which showed an adaptive function for hyperthermia and e) the highly regulated nature of fever which implies that fever must have developed as a host defense mechanism (19). Fever is further known to play a role in the suppression of microbial growth in iron-poor environments. It is also known to enhance a number of facets of the immune response such as stimulation of the expression of adhesion molecules that enhances leukocyte migration, proliferation of T cells, bactericidal activity of neutrophils and the pro-inflammatory cytokine profile (19,20,21). In addition, it is said to protect against the infection-induced disturbance of membrane lipids by phospholipase, and in so doing protect the integrity of membranes with regard to signal transduction and receptor expression (22).

The value of somnolence, another well-recognised characteristic of infectious diseases, is generally accepted, but poorly investigated. There are numerous studies to support the assumption of a negative effect of sleep deprivation on immunity, on neurohormonal activities and on behaviour. There is, however, very little research on the direct positive effects of sleep. One of the very few studies on the effects of excessive sleep showed increased NREM sleep to positively correlate with survival (23).

The behavioural effects of sickness behaviour largely correspond to those of depression. Similarities include fatigue, psychomotor slowing, anorexia, lethargy, suppression of certain cognitive abilities such as thinking and concentration, low interest in socializing and reproductive activities, as well as anhedonia. It is therefore not surprising to learn that the same cytokine profile is seen in the majority of patients with severe depression. In fact, the immunological profile of severe depression would further appear to be similar to that of the acute phase reaction, including the increases in plasma complement factors, increases in positive acute phase proteins, decreases in negative acute phase proteins, changes in T-cell numbers and activity, the release of inflammatory mediators, and many other similarities (24.25). The adaptive advantage of cytokine-induced depression during infectious disorders probably lies in the fact that it forces the individual not to get involved in activities which will test his or her coping abilities, to slow down, and to conserve energy expenditure for the adaptive febrile response and for immunological activity (26,27). The suppression of eating and reproductive behaviours are said to reduce the intake of nutrients (especially iron) necessary for the proliferation of the pathogen, and to prevent conception in the sick female individual – a risk factor for abortion and abnormal development (27). It should be stressed that cytokine-induced sickness behaviour is not only initiated by infectious conditions, but can develop in many non-infectious general medical conditions. Cytokine-induced sickness behaviour is for instance known to manifest in some cases of chronic inflammatory and autoimmune diseases, neurodegenerative conditions and post-partum (27). It may even be initiated by psychological stressors, as will be seen later in this chapter.

The symptoms of sickness behaviour may very well underlie some of the neuro-behavioural changes seen as poor patient compliance or illness behaviour - a personality and culture-dependent behavioural when ill. It is, however, important to remember that sickness behaviour and illness behaviour are two separate, albeit interacting, entities.

7.1.4 Control of sickness behaviour

Cytokine-induced sickness behaviour is of significant adaptational value, but unwarranted continuation of this syndrome has a serious down side. It is therefore of great importance that infection-induced synthesis and activity of pro-inflammatory

cytokines be strictly controlled and limited to the period of the disease. The short-term effects of severe, uncontrolled activity on multiple organ functions are well known. However, mild to moderately increased pro-inflammatory cytokine activity after recuperation from the infectious condition has its own problems. Such continued activity of the pro-inflammatory cytokine response can lead to cognitive and emotional problems, as well as to other psychological and physical symptoms that can impair the quality of life. Cognitive and emotional effects include the inability to concentrate, irritability, bad temper, anhedonia, apathy, or even anxiety and depression, while physical signs include symptoms like fatigue, headaches, swollen lymph nodes and sore throat (27,28). During prolonged severe sickness the behavioural patterns may turn into feelings of worthlessness, guilt and helplessness. Prolonged continuation of the symptoms of sickness behaviour has on occasion been implicated in the post-viral fatigue and chronic fatigue syndromes (27,29) and many sufferers would support the idea of the presence of feelings of worthlessness and helplessness in these conditions. More severe psychiatric/psychological effects of cytokines have been described in the previous chapter and it is thus theoretically possible that a continued high level of cytokines as a result of non-termination of sickness behaviour may have similar effects. The importance of termination of the inflammatory response upon recovery from the initiating disturbance is therefore abundantly clear.

Several substances are involved in the control of pro-inflammatory activity, including the anti-inflammatory cytokines, glucocorticosteroids, ADH, α-melanocyte stimulating hormone, the SAM-axis and certain members of the interleukin-1 family (5,30,31). The molecular mechanisms involved in containment of the sickness response are sometimes referred to as the cryogens (32). The role of the glucocorticosteroids are generally that of normal negative feedback. The HPA-axis, as previously mentioned, is stimulated by pro-inflammatory cytokines. The glucocorticoids thus secreted can in turn control the cytokine-induced effects a) by down-regulation of pro-inflammatory cytokine synthesis and release through inhibition of transcriptional and post-transcriptional expression of the IL-1β gene and decreasing the stability of the IL-1β mRNA, b) by decreasing the ratio of type I IL-1 to type II IL-1 receptors, and c) by suppressing the conversion of proIL-1β to

its biological active form through inhibition of the IL-1β converting enzyme (30, 33,34,35). ADH, a substance that acts in synergism with CRH, as shown in Chapter 5, is also involved. Fever-induced ADH secretion has, for instance, been shown to limit the suppressive effect of IL-1β on the behavioural functions (33).

Failure of any one of the factors involved in terminating the inflammatory process can contribute to the continuation of the sickness behaviour. An interesting phenomenon is the fact that the pro-inflammatory cytokines themselves can contribute to the continuation by inducing glucocorticoid resistance. Interleukin-1α was, for instance, shown to suppress glucocorticoid translocation and glucocorticoid-mediated gene transcription (36) and consequently inhibit the negative feedback on the production of pro-inflammatory cytokines.

There are indications that some antidepressant drugs may be successful in the treatment of the cytokine-induced depression (27,36). Whether this is mediated through a suppression of the induction of pro-inflammatory cytokines by activated immune cells, glial cells or neurons, or through their effects on the cytokine-induced changes in the neurohormonal activity is, in many cases, still under investigation. This aspect will be returned to at a later stage.

To summarise this writing on sickness behaviour, it can be said that sickness behaviour is a good practical example of the psychoneuroimmunological interaction. It should be seen as a new mind-body homeostasis – a functional homeostatic adaptation caused by the induction of pro-inflammatory cytokine production in the brain, rather than a debilitating side effect of infectious diseases. However, if this pro-inflammatory activity is not terminated after recuperation from the infectious condition it may lead to emotional, cognitive and physical problems that can impair the quality of life.

In the previous chapter it was shown how peripheral immunological events can stimulate central nervous system cytokine production with subsequent changes in the neuroendocrine systems and an eventual new mind-body homeostasis in which the

physical and psychological changes are intended to aid in coping with the stressor – the stressor in this case being the infectious condition (Figure 6.1, Chapter 6). This diagram can now, based on the discussion of sickness behaviour, be extented into a schematic presentation of sickness behaviour in psychoneuroimmunological context (Figure 7.1). Figure 7.1 shows how infection can, through the induction of cerebral cytokine production, lead to changes in central nervous system activity and alterations in stress system set points. This could then shift the total mind-body homeostasis to a sickness behaviour homeostasis, which includes adaptations in neurohormonal functioning, behaviour, metabolic and motor function, as well as adaptive immunological alterations. Upon recuperation from the infectious affliction, anti-inflammatory cytokines, glucocorticoids, ADH and several other factors are involved in the termination of the immunologically induced stress response, and return to the original homeostasis should occur. The symptoms of sickness behaviour can be seen at the bottom of the diagram. It is also indicated that once the stimulus is gone, i.e., the infection is cleared, factors that counteract the sickness behaviour symptoms by returning the neuroendocrine homeostasis to normal must come into action. Failure to do so may have serious physical and mental implications.

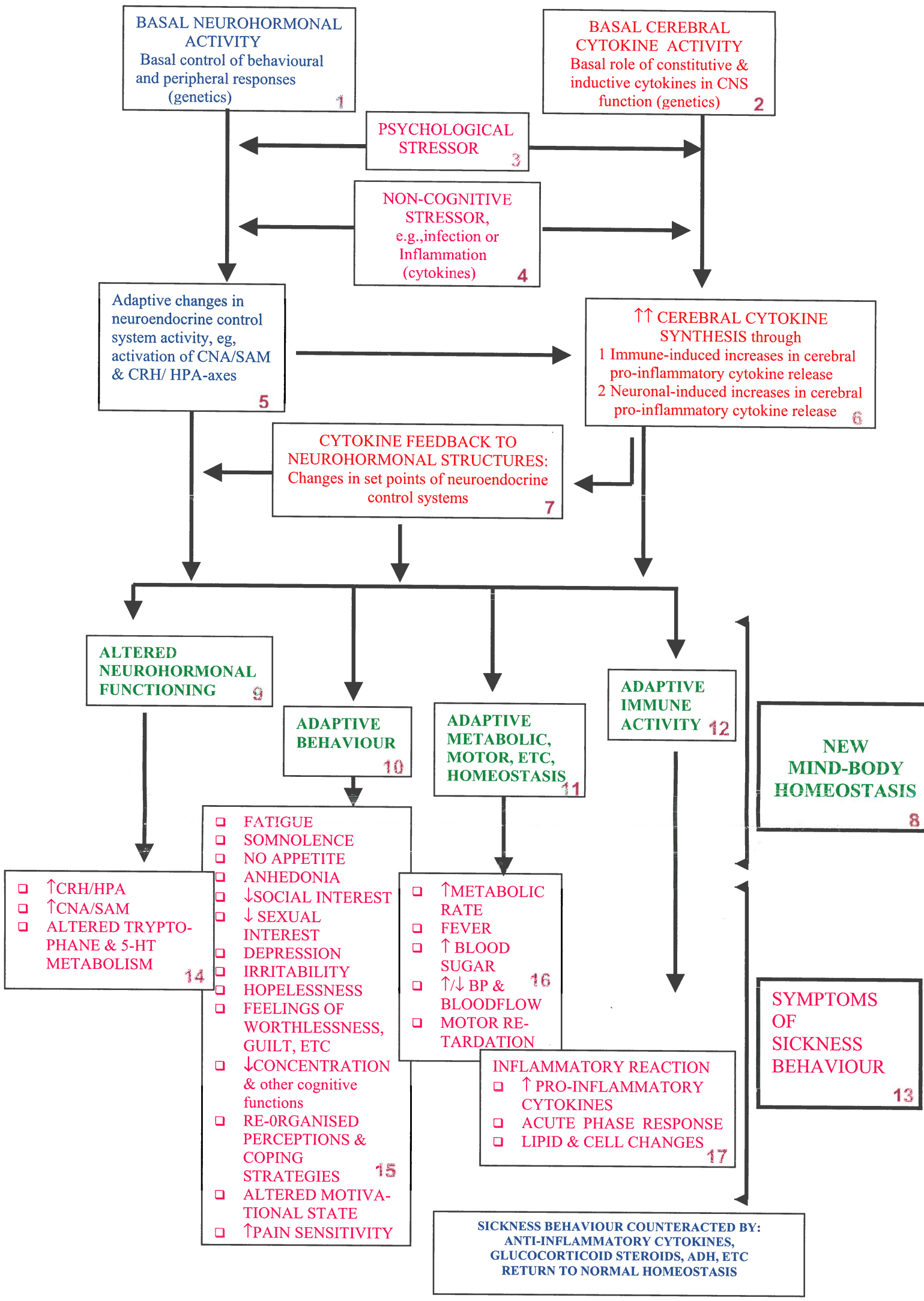

Figure 7.1: Sickness behaviour in psychoneuroimmunological perspective.

[1 and 2 represent the basal neurohormonal and basal immunological activity of the brain.These basal activities can be stimulated both by psychological sressors (3) and, as the case of infections, trauma and inflammatory conditions, by peripherally derived cytokines (4). The increase in basal neurologicical activity (5) would induce further cerebral cytokine production. Cerebral cytokine production is thus increased (6) as a result of peripheral immune activity as well as the increased neuronal activity. The marked increase in cerebral cytokine activity (6) can in turn feedback to the neurohormonal systems to bring about changes in their set points (7). The altered cerebral neurohormonal and cytokine activity will lead to a new adaptive mind-body homeostasis (8) intended to help cope with the stressor. Components of the new adaptive homeostasis include altered neurohormonal functioning (9), adaptive behavioural functions (10), adaptive metabolic and motor function (11) and adaptive immunological activity (12). The symptoms specific for the adaptive homeostasis of sickness behaviour (13) are shown in 14, 15, 16 and 17.]

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Legend to Figure 7.1

Figure 7.1: Sickness behaviour in psychoneuroimmunological perspective

[1 and 2 represent the basal neurohormonal and basal immunological activities of the brain. These basal activities can be stimulated both by psychological stressors (3) and, as the case of infections, trauma and inflammatory conditions, by peripherally derived cytokines (4). The increase in basal neurological activity (5) would induce further cerebral cytokine production. Cerebral cytokine production is thus increased (6) as a result of peripheral immune activity, as well as by the increased neuronal activity. The marked increase in cerebral cytokine activity (6) can in turn feedback to the neurohormonal systems to bring about changes in their set points (7). The altered cerebral neurohormonal and cytokine activities with the new set points, will lead to a new adaptive mind-body homeostasis (8) intended to help cope with the stressor. Components of the new adaptive homeostasis include altered neurohormonal functioning (9), adaptive behavioural (10), adaptive metabolic and motor function (11) and adaptive immunological activity (12). The symptoms specific for the adaptive homeostasis of sickness behaviour (13) are shown in 14, 15, 16 and 17.]

It is, as previously mentioned, essential that sickness behaviour be terminated at the appropriate time in order to prevent secondary behavioural effects. Before addressing the consequences of a failure in the correct negative feedback mechanisms for mental health we must first ask whether the vulnerability of the CNS cytokine-neuroendocrine mechanisms responsible for the sickness behaviour is dependent merely on the qualities of the initiating stressor and the genetic disposition or whether predisposition to either the development or inappropriate continuation may occur as a result of previous life experiences. These aspects will be addressed in the following sections.

7.2 The influence of early life experience

In Chapters 4, 5 and 6 it was shown that a bidirectional influence exists between the basal neuroendocrine and the basal immunological activities of the brain. Should either of these basal processes be altered by early life experiences, or rather by previous life experiences, it speaks for itself that deviations from the norm could develop and that it may even predispose to what is artificially separated into physical and behavioural disorders. In Figure 7.2 it is asked whether such changes can indeed develop.

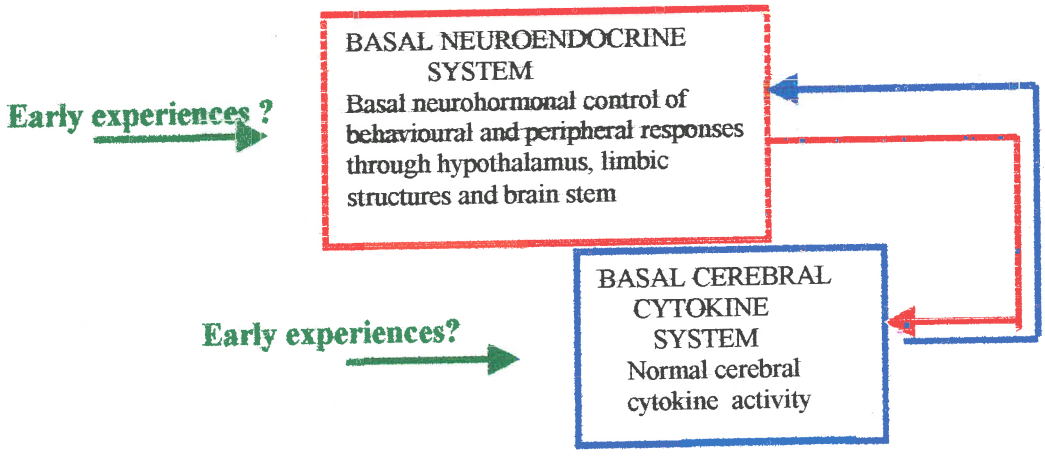

Figure 7.2: Can changes in the basal responsiveness of the neuroendocrine or cerebral cytokine systems predispose to mental and physical disorders?

The next two sections will show that early life experiences can change the basal neuroendocrine activity of the two main stress axes as well as the basal activity of the immune system and by implication predispose to physical and psychological abnormalities.

7.2.1 The effects of early life experiences on the neuroendocrine systems involved in behaviour

Genetics are known to have an influence on behaviour, but it is also widely accepted that early psychosocial life experiences can have a marked impact on the psychological wellbeing of adulthood. The latter is sometimes referred to as the non-genetic transfer of behavioural characteristics. The influence of early life experiences on the stress axes-related neuroendocrine systems involved in behaviour were already touched upon in previous chapters where the psychoneurological interactions were discussed in terms of the two main stress axes. The emphasis was, however, to some degree on the structural changes of the brain as a result of unfavourable environmental conditions rather than on the long-term implications for psychological and physical health. In general there can be no doubt that adverse psychosocial experiences during early life will have negative effects on both the physical and the psychological adaptations and health. These negative consequences are largely the reflections of alterations in the neuroendocrine structure and function. In short, one can say that infants are born with a genetic predisposition (37), which will partly determine their adult behavioural responses as well as the type of pathology they may develop when under severe or continuous stress (38,39). However, in addition to the genetic-make-up, early rearing experiences fundamentally influence the outcome by priming the individual to react in certain ways in the face of a stressor. The next couple of paragraphs will deal with environmental predisposition of the two main stress axes during early life and will show that small variations in early rearing experiences may have a marked impact on adulthood stress responsiveness.

It is of great importance to know how infants are primed, in other words predisposed to specific behavioural patterns and disease susceptibility during adult life. Within this context the primary caregiver and the early family environment are critical in modulating

the infant's physiological arousal state and serve as major source of vulnerability during adult life. It largely determines the development of the infant's long-term stress response – a factor that will eventually determine the degree of stress vulnerability or resistance (40). Various factors play a role in determining the eventual stress vulnerability of the individual, including the nature of the cortical networks formed during critical stages of brain development. It is known that normal brain development and maturation require external stimulation for the formation of the appropriate cortical networks (41). These cortical networks are initially formed by the overabundant production of synapses – which are then sculpted by a process of parcellation, i.e., activity-dependent fine-tuning of connections and loss of excess circuitry (42). It is here that early experiences are critical. Early experiences determine the circuit wiring of, amongst others, the orbitofrontal cortex, which in turn contributes to the regulation of the responsiveness of the stress response – including the responsiveness of the autonomic nervous system – and monitors and adjust emotional responses (43). Environmental stressors can lead to dysregulated stress hormone levels in the brain that may give rise to pathomorphogenesis (43). During these critical periods of maturation developing neurons will establish or maintain aberrant connections, or even die, if the infant is subjected to severely adverse rearing experiences. This may lead to impaired cortical control over behaviour. The process may very well also apply to *in utero* stress where maternal stress influences the foetus. In addition, abnormal seizure-like activity (kindling) may occur. This could have a hyperactivating effect (42,43). As discussed in Chapter 2 and 3, and previously mentioned in this paragraph, these external influences may, in addition to their influence on morphological properties further influence the secretion of central nervous system neurotransmitters which will have a further influence on neural development and plasticity (41).

As this thesis focuses on psychoneuroimmunology in terms of the two main stress axes, it is relevant to look at the influence of early life experiences on the structures and functions pertaining to these systems. It would indeed appear as if the neural structures of the CNA/SAM-axis and CRH/HPA-axis are of paramount importance in the predispositioning to stress vulnerability or stress resistance. This is not surprising if one

takes into account the key role they play as neuromodulators of cerebral cortex, limbic system and autonomic function. The importance of the CNA/SAM-axis in the behavioural functions and its interactions with other neuronal structures that play a role in emotions and cognition, i.e., the psychoneurology of the system were discussed in Chapter 3. The potential impact of early rearing experiences on adult life can, in fact, easily be understood from the details presented in Chapter 3. It was, amongst others, shown that the CNA/SAM-axis

- can be presensitised by adverse environmental conditions
- plays a role in fear conditioning and in the recall of adverse events
- is susceptible to modulation and modificaton by environmental and psychosocial influences, i.e., stress adaptation and presensitisation
- can, through stress-induced noradrenaline secretion, modulate gene expression
- is involved in behavioural adaptation to stressors and can through such experiences be instrumental in the development of functional, as well as dysfunctional coping skills
- can be linked to personality characteristics
- activity would appear to differ between children with different temperaments - with high autonomic threshold and quick return to baseline in the so-called easy child and the reverse situation with a high predisposition for reactivation in the so-called difficult child
- plays a role in the development of fear and anxiety disorders
- is associated with several behavioural characteristics and disorders marked by a variety of dysregulations in central noradrenergic activity
- has a pervasive interaction with other systems involved in cognition, emotions and stress sensitivity
- abnormalities occur with concomitant dysregulations in other neuroendocrine/behaviour modulator systems – reflecting a multidirectional interaction between the systems
- is vulnerable to modulation of its structure and functions by psychological processes such as thoughts and perceptions

- is a target for psychological experiences that can serve as biological response modifiers and in so-doing influence the central noradrenergic system by, amongst others, changing the variable gene expression of the system – a phenomenon of importance in perinatal learning. as well as adaptational development and modification
- demonstrates differences between the effects induced on its structure and functions by controllable *versus* the effects induced by uncontrollable stressors - effects that are very much dependent on the type of perception the individual has about a potential stressor.

Studies on the CNA/SAM-axis very often include the rest of the autonomic system, culminating in investigations that focus on the autonomic balance and its interactions with other brain structures. In general, there seems to be a link between the orbitofrontal cortex, hemispheric dominance, autonomic control – specifically the degree of sympathetic dominance - and early life experiences. This is markedly evident with regard to the attachment experiences of the young. It would appear as if proper integration between left hemispheric functions (verbal coping, etc) and right hemispheric function (emotionality), in which emotions originating from the right hemisphere are recognised and dealt with by the left hemisphere, must develop in order to remain physically and emotionally healthy. It seems that individuals who intellectualize, but ignore their emotions (left dominant) tend to develop physical illness, while those who feel (right dominant) but cannot work through their emotions, lean towards the development of mental problems (42,43,44,45). In addition, development of the right balance between sympathetic and parasympathetic responsiveness is important for emotional wellbeing and a mothering style that leads to a secure attachment between mother and infant is said to be a major determinant in the development of this autonomic balance. In this development the orbitofrontal cortex with its connections to just about all other regions is of major importance. The orbitofrontal cortex receives input from all sensory associations, has an output to motor areas, and projects extensively to limbic areas (42). Two limbic circuits exist. The first, i.e., the excitational ventral tegmental limbic system, (encompassing the anterior cingulate, insula, temporal pole, central nucleus of the

amygdala, olfactory areas, glutamate responsive NMDA receptors of mesocorticolimbic dopamine neurons in ventral tegmental areas of the anterior reticular formation and centres in the paraventricular nucleus of the hypothalamus), is associated with CNA/SAM-axis activation (42). The link between the sympathetic nervous system and the paraventricular nucleus (CRH/HPA-axis) has been discussed in previous chapters. The second, i.e., the inhibitory lateral tegmental limbic circuit (innervating noradrenergic neurons in the medulla, and the vagal complex in the brain stem caudal reticular formation) stimulates the parasympathetic areas of the hypothalamus (9). If the excitational limbic circuit is damaged by extensive parcellation during early life, the inhibitory limbic circuit, and thus the parasympathetic component of the autonomic nervous system, will be dominant (42,43). Parasympathetically mediated passive coping is said to be driven by the inhibitory limbic circuit and leads to withdrawal directed towards reduction of the emotional impact of stress (42,43). Such individuals will, in adult life, show reduced overt emotionality, but inefficiency in regulating high arousal states under stress conditions. They will be vulnerable to overregulation and internalising psychopathologies (42,43). Conversely, damage of the inhibitory circuit will lead to sympathetic dominance, leading to a susceptibility to underregulation and externalising psychopathologies. Under severe stress, both these circuits may be in a state of activation, leading to increased sympathetic and parasympathetic outflow (42,43). In ideal circumstances, both sympathetic and parasympathetic outflow would be low. Optimal health will thus ensue when left and right hemispheres are integrated, and all autonomic outflow is low. At this stage in time it would appear to be the most probable outcome of sensitive responsive mothering.

It is feasible to suspect that certain patterns may exist according to which individuals could be classified on the basis of their hemispheric and autonomic dominance and that early life experiences may play a role in the development of these patterns. In line with this, intellectualising persons (left hemisphere dominant) with sympathetic dominance will typically suppress their negative emotions like anger and unhappiness and be prepared to take responsibility (46,47). At some stage in their lives such people are bound to feel helpless (45,47) – a feeling which, in chronic context, is often associated with

depression. A possible contributing factor to left hemisphere/sympathetic dominance would appear to be a rearing style of conditional love, i.e., affection shown only when the child is ill or 'good' (49,50).

Intellectualising persons with parasympathetic dominance would appear to have learnt to suppress most emotions successfully. They are externally driven, with the workaholic as prototype. In addition, they often are compulsively self-reliant, accordingly do not feel helpless, and thus do not secrete excessive amounts of cortisol (51). The humoral immune system of these individuals is usually overactive, and allergies and autoimmune diseases commonly occur in this group (46). Because these persons are usually relatively unaware of their emotions, they may interpret their physical manifestations of anxiety on a purely physical basis, e.g., palpitations, light-headedness and an inability to swallow. They therefore may be diagnosed with somatisation (44,49). Maternal neglect would appear to play a role in the genesis of the above disorders.

If children are exposed to severe physical or sexual abuse in the critical period of brain maturation, the stress overload may lead to limbic kindling, with resultant increased sympathetic as well as parasympathetic outflow, experienced subjectively as emotional chaos (42,52). One way of coping with these extreme experiences would be to shut off emotions completely, and dissociate. Post-traumatic stress disorder (PTSD) and several dissociative disorders would seem to fit into this category. Dissociation in this context has an adaptive function by allowing a person not to become overwhelmed in the face of trauma (53). Imaging studies have shown that combat-related PTSD leads to smaller right hippocampal volumes, and thus presumably dominance of the left hippocampal system (54). The latter assumption may, however, not necessarily be extrapolated to what is conventionally seen as dissociation disorders. Interesting work in this context show that in individuals with depersonalisation disorder (dissociation disorder with anxiety, where behaviour is sometimes referred to as *thinking without feeling)* aversive events appear to activate mainly the right ventral prefrontal cortex (an area associated with emotion regulation), with very little activation of the insula and occipito-ventral cortex (areas associated with perception or emotion-sensitivity) (55).

The picture appears somewhat different when we look at those individuals who are aware of what they feel, i.e., right hemispheric dominance. These "emotional" individuals are more likely to develop psychiatric than physical disorders. Emotional persons with sympathetic dominance typically feel anxious, the rearing style to which they were subjected often characterised by unpredictability (50), and their early experiences marked by a feeling of diminished control - a known risk factor for later anxiety (53,56). Anxiety disorders, panic disorders, obsessive-compulsive disorders, and histrionic and schizotypal personality disorders seem to fit into this category. For example, studies have shown that persons with panic disorder had more often experienced early loss of a caregiver or extremely inadequate caregiving, and persons with agoraphobia reported more early separation from their mothers as well as parental divorce (53).

Persons who are aware of their emotions but with parasympathetic dominance are said to be characterised by feelings of anger or emptiness. Eating disorders, substance abuse, conduct disorder, depression and narcissistic, borderline and antisocial personality disorders would seem to fit into this category. Maternal rejection and/or sexual abuse may be common features of this group. It is for instance well known that sexual abuse is extremely common in the histories of patients with borderline personality disorder (53). Imaging studies have shown that severely sexually abused women have smaller left hippocampal volumes, and thus presumably dominance of the right hippocampal system (54). Antisocial personality is associated with harsh discipline, inadequate supervision, prolonged separation from caregivers, unaffectionate mothers and deviant fathers (53). Patients with eating disorders have a decreased ability to examine their own psychological states (which is a function of the left hemisphere), and divert distress by focussing on their bodies instead. Their parents typically indicated support, while actually undermining their daughters' confidence (53). Anti-serotonin and anti-dopamine antibodies may play a role in the eating disorders (57). There appears to be a significant genotype-environment interaction in the brain metabolism of serotonin, wherein the ultimate effect of a gene polymorphism is highly dependent on the specific early attachment experience of the individual (58).

Children with right-dominance who are exposed to severe emotional abuse (e.g. extreme humiliation) may not be able to cope, and simultaneous sympathetic and parasympathetic activation could occur (42). As these children become increasingly shut off from their reasoning capabilities (in the left hemisphere), they may tend towards psychosis (11). Chronic schizophrenics are said to have significantly reduced grey matter in the left anterior hippocampal-amygdalar region (45). Furthermore, children at high risk for schizophrenia, have been reported to show left-sided movement abnormalities when challenged, reflecting overactivity of ascending dopaminergic systems in the right hemisphere (42).

From the discussion above it is clear that the sympathetic nervous system can, in association with other systems be programmed by early life experiences, especially by the influence of mothering style on the infant and child. In short, it is probably correct to say that optimal health ensues with integration of reason and emotion, i.e., with the appropriate hemispheric dominance and with low basal autonomic outflow – sympathetic as well as parasympathetic. It has, however, in Chapter 5 been shown that the central nervous system CRH neurons can to a large extent control, amongst others, the sympathetic nervous system and central noradrenergic activity. In view of this, as well as the fact that the CRH/HPA-axis represents the other major stress axis, the next couple of paragraphs will briefly deal with the way in which early life experiences can program adult neuroendocrine and behavioural responses through early influences on the CRH/HPA-axis. It should, however, be remembered that a reciprocal positive feedback exists between the CRH and noradrenergic systems and that activation of the one will in general lead to activation of the other (Chapter 3). It has, for instance, previously been mentioned that the CRH neurons of the hypothalamus are important targets of noradrenaline and that CRH in turn activates adrenomedullary catecholamine release (discussed in Chapter 3 and Chapter 5).

Chapter 5 demonstrated the central role of CRH in psychoneuroimmunology in terms of the two main stress axes. It was shown that both cortisol and CRH are of major importance for most adaptational events and that stress-induced changes in the regulatory

feedback mechanisms could have serious implications for the individual. It is obvious from the details presented in previous chapters that long-term alterations of the system could have far-reaching effects on the ability of the individual to cope with future life stressors and that it may predispose to both physical and behavioural problems.

Recent research indicates that the CRH/HPA system may be the major target through which adverse events in early life can predispose the individual to physical diseases and psychological abnormalities in later life. The supporting evidence to this effect is overwhelming and very much a topic of the day. The most important psychosocial variables involved with early life stress-sensitisation of the CRH/HPA-axis would again appear to be the nature of maternal care and the influence of the direct family environment. A comprehensive discussion of how variations in maternal care can regulate the development of stress reactivity would be far beyond the scope of this work and only some of the more salient points of evidence are therefore referred to. As most of the facts mentioned have been confirmed by the work of several different research groups many of the original workers are not referred to in this text. The following facts have been firmly established through empirical research

- Mental as well as physical disorders generally result from high levels of environmental demands superimposed on an underlying susceptibility or vulnerability. Susceptibility is, in turn, a function of both the genetic make-up and earlier life experiences that caused long-term alterations in neuroendocrine systems such as the CRH/HPA-axis and the noradrenergic system – the very same systems necessary for adaptation and coping. It is at this stage necessary to stress that severe abuse is not necessarily needed for high stress sensitisation, but that factors such as emotional neglect, poor infant-parental bonding, a cold or distant/detached family environment, periods of maternal separation and other relatively common occurrences can all alter the basic neuroendocrine-behavioural responsiveness and as such predispose to the development of mental and physical abnormalities in adult life – especially to those disturbances associated with the two main stress axes (59). It is

again to be stressed that presensitisation of the two axes can, as a result of their reciprocal activation, barely be distinguished between.

- Sensitive mothering with optimal positive physical contact between mother and infant can lead to a moderate HPA-response to aversive stress exposure and increased hippocampal negative feedback (increased hippocampal glucocorticoid receptor mRNA expression and decreased hypothalamic CRH mRNA) during adult life (60).
- Natural variations in maternal care give rise to individual differences to stress-induced HPA-axis-related behavioural responsiveness in adult life by its early effects on CNS systems such as forebrain noradrenergic activity that activate the HPA system or inhibit the GABA mechanisms (60).
- The offspring of mothers who demonstrate less contact and less positive mothering (as opposed to those who demonstrate optimal positive contact and sensitive mothering) show increases in the startling responses, lower exploratory behaviour in novel environments - in general greater fear of novelty and more severe stress responsiveness to any condition that may pose a potential threat (60,61)
- The adult offspring of mothers who show less favourable contact and less sensitive mothering behaviour (as opposed to those who demonstrate intensive positive contact and sensitive mothering) show higher CRH-induced central nervous system noradrenaline secretion (increased CRH receptor expression in the locus coeruleus and increased CRH mRNA expression in the central nucleus of the amygdala as well as decreased central benzodiazepine receptor expression in the amygdala and locus coeruleus) (60)
- Adults, who experienced favourable rearing conditions during early life do not only show a decrease in fearfulness, decreased mRNA in the PVN, and central nucleus of the amygdala in adverse circumstances, but also decreased CRH-content in the locus coeruleus – a fact that would lead to lower activation of the brain stem noradrenergic systems (59).
- Favourable rearing experiences do not only lead to strong negative feedback of glucocorticoids on the CRH/HPA system but also dampen stress-induced noradrenergic responses in the PVN (62).

- Longer periods of separation from the mother may change the neurohormonal profile of the infant or child in a way that may predispose to depression in adult life (increased CRH gene expression in the PVN and amygdala, altered noradrenergic and serotonergic pathways, decreased GABAergic/central diazepine systems activity - which regulate central CRH and noradrenergic activity) (63).
- Lactation blunts the neuroendocrine responsiveness to stress in later life. (Lactation reduces noradrenergic inputs to the PVN CRH neurons and may lead to phenotypic changes in neuropeptide expression, e.g., reduced expression of CRH mRNA and increased expression of ADH mRNA, reduced pituitary sensitivity to CRH and increased sensitivity to ADH). This may occur through lactation-induced alterations in the CRH neurons of the PVN, which then modulate the expression of neuropeptides and neurotransmitters in the BNST and the amygdala (64). Of interest is the fact that breast-feeding mothers have lower levels of ACTH, cortisol, ADH and adrenaline responses to stressful events than non-breast-feeding mothers (65). This could very well underlie the changes seen in the infant.
- Intergenerational transmission of maternal behaviour, i.e., non-genomic transmission of parental behaviour and stress responsiveness occurs from generation to generation and the stress responsiveness is transmitted by the nursing mother and not necessarily the biological mother. This intergenerational transmission is most probably mediated by the fact that mothers with low stress reactivity, reflecting their own favourable early life experiences, provide the type of maternal care that installs low stress responsiveness in their offspring (66).
- Maternal stress can have *in utero* influences on the offspring. Although it is unlikely that maternal CRH would pass through the placenta, adrenocortical hormones released in response to stress-induced CRH-release can cross the placenta and probably mediate the gestational stress which leads to short-term, as well as long-term morphological and behavioural changes in the young (67).
- There can be no doubt that stress-induced alterations in the CRH system can occur as a result of early life experiences and that this can persist throughout adult life. It is also known that alterations of the CRH system are present in depression and in anxiety disorders (elevated), in stress-related disorders such as posttraumatic disorder,

Tourette's syndrome and obsessive-compulsive disorders (elevated), during fearful behaviour with high frontal brain electrical activity (elevated), and in suicide victims (elevated), and that this may, partially at least, result from the influence of early childhood experiences (68). Valuable information to this effect has been obtained through molecular biology and genetic engineering techniques.

- Evidence exist that separation stress in the young may, by increasing CRH neurotransmission in the raphe nuclei, alter serotonin activity and receptor expression in adult life (69). Changes in hippocampal cortisol receptors as a result of adverse early experiences have, in turn, been reported to be dependent on serotonin activity (70)
- In general it would appear as if favourable rearing experiences will lead to decreased pituitary-adrenal responses to stress, enhanced glucocorticoid receptor binding in the hippocampus (both pointing towards a down-regulation of the stress response), increased synaptogenesis in the hippocampus with good development of memory consolidation ability, decreased CRH mRNA expression in the hypothalamus with moderate stressor responsiveness, as well as decreased CRH receptor expression, increased presynaptic alpha-2-adrenoceptors and increased benzodiazepine receptors in the amygdala and locus coeruleus of the adult – all factors that contribute to protection against excessive vulnerability to stress-associated disorders and reactions. (71).
- There is evidence to believe that during the early stages of brain development CRH neurons may be involved in target recognition and synaptic organisation – the implication for abnormal CRH activity with regard to cerebral organisation is frightening (72).
- Inflammatory conditions during early life may also change CRH/HPA-responsiveness in adult life. (73). This is in agreement with the fact that immunological events can produce a central nervous system stress response similar to that initiated by psychological stressors – as discussed in Chapter 6.

This section provided evidence to support the assumption that early life experience can lead to alterations in the structure and function of the two main stress axes and in so-

doing predispose to abnormal reactivity to potential stressors during adulthood. It was shown how, by altering the receptor expression, the degree of negative feedback and other functions, the vulnerability of the two main stress axis can be predisposed to either hyper- or hyporesponsiveness to stressors. This section thus provided the empirical evidence that adverse early childhood experiences can alter the basic neurological structure, function and sensitivity of the brain in a way that it can be expected to react to the onslaught by psychological, physical and immunological stressors in a way different from that of individuals with more favourable early life experiences. It should again be stressed that differences can be induced by subtle variations in early life experiences and not necessarily only by overtly abusive situations. The question remains whether one ideal developmental pattern really exists for the stress systems as various environments may require different degrees of responsiveness during adult life.

7.2.2 The effects of early life experiences on the immune system

In Chapter 2 it was demonstrated that links exist between the immune status and all categories of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and that inflammatory conditions would often appear to be present in mental disturbances. A link was also described between the psychoimmunological relationships and cerebral laterality – a phenomenon shown, in the previous section, to have some bearing on early life experiences. In a short introductory overview in Chapter 2 it was seen that early life experiences might influence the immune status of adult life. The underlying mechanisms were largely ignored at that point. In Chapters 4 and 5, the mechanisms through which the two main stress axes can influence the immune system were discussed, but early childhood experiences were not dealt with. Chapter 6 dealt with the pathways through which immunological events can influence neurobehavioural functions. The following couple of paragraphs will now show the type of early childhood experiences that may predispose to immunological vulnerability in adult life and the role of the stress axes in this phenomenon.

In humans, most such studies are of a correlation nature, as relevant experimentation can for ethical reasons not be performed. It is, however, known that a significant part of the

results from animal experimentation do not necessarily apply to humans. Due to similarities in social relationship characteristics, the best extrapolations to humans can probably be made from non-human primate experimentation (74). The experimental evidence provided below will mainly be that derived form non-human primates with some evidence coming from human studies. Extrapolations from primates show that

- There is a strong maternal influence on the development of circadian rhythms in the offspring. In some species, the maternal zeitgeber function can be fulfilled by a conspecific female, but this is not always the case (75,76). The influence of disturbed circadian rhythms on immune development is well known and has been referred to previously.
- Differences in the development of the stress and other behavioural responses, as a result of variations in the mother-infant bond, points towards long-term effects on the immune system. Inconsistencies in the degree of maternal protectiveness, as well as rejection and inattentiveness have been shown as major tension-producing factors in the mother-infant relationship – eventually leading to deranged affiliative behaviours and social subordination, as well as higher levels of separation distress at a later stage in life (77,78). Similar exaggerated separation distress resulting from maternal rejection, inconsistencies or unresponsiveness, with subsequent abnormal stress coping behaviour during adult life, can develop in humans.
- There is enough evidence to show that nursery rearing of non-human primates and humans may lead to different immunological profiles from that of maternally raised individuals. This is but one form of separation stress and the acute immunological effects in animals other than primates were discussed in chapter 4. The effects of separation stress do, however, depend on the age the infant is removed from the mother and on other factors such as the degree of peer interaction. The main factor would appear to be the degree of emotional isolation. In some studies only the neurohormonal profiles of these adults were investigated, but, in view of the immune influences of these substances, as shown in previous chapters, it can with a fair amount of certainty be presumed that immune function would be abnormal (79,80,81). Interesting results are derived from studies where non-human primate

infants were handreared by humans. Although very few negative behavioural effects could be detected, long-term immunological changes, especially in response to mitogen-stimulation were observed - with continuation of the effects determined by the age of the initial separation from the mother (82,83,84). Although very little work was done on humans it can with confidence be said that normal mother-infant, as well as peer interaction is necessary for normal immunocompetence in the adult life of non-human primates. However, this type of study can easily be performed in humans by retrospective investigations of child rearing in combination with prospective investigation of the immune status and reactivity.

- Transient disruption of the mother-infant bond by temporary separation, even at an age where the non-human infant can already survive without the mother, still has deleterious effects on the immune system. The behavioural effects of such transient periods of separation are well known. These usually include initial vocal protestations followed by withdrawal if the separation is prolonged (85,86). The physiological changes would in general appear to be mediated through concomitant activation of the two main stress axes, as evidenced from an increase in sympathetic activation and elevated cortisol levels, and seem to covary with the degree of behavioural distress (87,88,89). Immunological effects are very often present and the vulnerability to infections, as would be expected, very often increased in parallel with heightened sympathetic nervous system and HPA-axis activity, as well as with behavioural changes (90,91,92,93,94). Although one could speculate, it would be of great interest to have empirical information about the effects of early admissions to nursery schools and day care centres on the immune system of the human infant. In the non-human primate the separation reactions, psychological as well as immunological, would appear to depend on prior mother-infant bonding – a factor of great importance in the development of later social separation vulnerability. Other factors such as variations in the form of social support, maternal dominance status, infant gender, infant parity and genetics, may, however also influence the outcome. At this stage it would appear that the outcome is largely dependent on stress axis presensitisation, which has a major role in both the immunological and the behavioural predisposition. In view of this and other observations, it has been suggested that baseline values of HPA- and

SAM-axis activity may perhaps be used as prognostic indicators of high risk for the development of both infectious and behavioural problems in later life (95). A small number of studies exist that corroborate similar predispositions in humans. Children with exaggerated baseline neurobehavioural response patterns have been reported to be at higher risk for the development of immunological diseases such as allergies and those with a blunted responses at a higher risk for the development of autoimmune diseases (96,97). Behavioural response patterns have also been linked to antibody titres such as that against cytomegalovirus, but more work is necessary for it to be conclusive. Although maternal separation, even transient separation, can have harmful effects on the immune system these effects can be buffered by substitute caregivers (98,99). This is applicable even during recovery from the common cold (100).

- Disruption of peer bonding, especially following upon maternal separation, has long been known to have a behavioural impact. This is also the case for immunocompetence and the two types of disturbances may very well run in parallel. The most marked peer separation disrupting effects on the immune system are seen upon multiple peer separations (101,102).

More work is needed to come to a clear understanding of the effects of separation distress on the eventual immune status of adulthood. What is, however clear is that, as in the case of the behavioural effects, it can have long-term consequences. The long-term consequences are to a degree modulated by other factors, including mother-infant bonding should reunion occur after a period of separation (103). Separation with subsequent augmented maternal care upon reunion had been implied to have the potential to lead to a stronger immune system in adult life. The consequences of repeated transient separation and reunion as occur with parents with busy professional lives, as well as with family disruption due to unfortunate socio-economic circumstances, are not known. There is however, plenty of evidence to show that permanent separation without adequate surrogate bonding will predispose to immunological-related disorders such as immunodeficiency, leukopenia and other malignancies (104), as well as to behavioural disturbances. These behavioural effects and immunological predispositions covary and it

can, with almost certainty, be said that they are to a large extent secondary, at least at effector level, to alterations in the CRH/HPA-axis. As most of the immune changes would essentially be modulated through neuroendocrine influences, it is feasible to extrapolate predictions from known neurobehavioural changes.

Predisposition to abnormal immunocompetence, as is the case for the behavioural functions, can also occur as a result of socio-environmental influences during adolescent and adult life – even in later stages of adult life. Disruption of social bonds, as well as rehousing may lead to marked alterations in behavioural and immunological parameters – again accompanied by changes in HPA-axis activity. The HPA-activity is usually one of hyperactivity, depending on the degree of adverse emotionalility experienced (105,106,107,108). Housing relocation in association with infectious complications may even increase morbidity and mortality (109). Relocation with subsequent lowering of social dominance or ranking and a decrease in affiliative behaviour may similarly have very serious implications for future immunocompetence (110,111). Even reintroduction into the previous social group may have grave consequences as seen by increased HPA-axis activity and a decline in CD4+ and CD8+ counts. The magnitude of the effects would often appear to be dependent on the degree of competitiveness and the presence of aggression (112). Similar changes have been reported in conditions with social instability due to constant reorganisation or changing of the environment. Here again the immunological effects appear to depend on alterations in social ranking and behavioural patterns such as affiliation and aggression, as well as other variables in the social interactions. Experimental work clearly showed that constantly changing social conditions and venues of social interaction might impact on the progression of immunological-related immune disorders (113,114). As would be expected, an influence for competitiveness on immune responsiveness has been shown. The degree to which subsequent life stages are influenced is not clear, but with the nature of the neuroendocrine control on the immune system, discussed in previous chapters, it can be assumed that it would depend on the period of exposure, as well as the intensity, i.e., whether permanent neuroendocrine alterations have been induced. Although dominance would not appear to be directly related to the degree of immunological alteration, losing

out on opportunities has been shown to have significant negative effects on especially the B-cell immunological responsiveness (115). Disruption of the social environment by, for instance, the introduction of an aggressive male, has been shown to impact on the immunocompetence – especially of females who become the recipients of the aggression (116). It is very tempting to speculate about the effects this factor may have in the work place, but many factors will have to be considered in such a study, not least prior priming and attitudes of the resident human female population.

It is, in short, feasible to extrapolate from experimental results obtained on non-human primates that, as in the case of behaviour a) immunological competence is influenced by early life psychosocial experiences, b) these early influences may predispose to immune-related disorders in later life, c) the main stress axes and especially the CRH/HPA-axis are involved in the immune alterations, d) baseline activity of the two main stress axes may be prognostic indicators of vulnerability to immune dysfunctions, and e) positive affiliative interactions may ameliorate the adverse effects of negative early life experiences on the immune system and through this once again on behaviour.

7.2.3 Mechanisms underlying the predisposition to stress hyperresponsiveness, hyporesponsiveness and stress resistance.

It is not completely clear how predisposition to high stress vulnerability develops. Some of the changes that could lead to a low threshold value for the two major stress systems, i.e., changes that would increase the stress responsiveness, and potentially lead to excessive reactivity, as well as behavioural and physical disturbances, were described in the previous paragraphs. They include a) pathomorphogenesis as a result of stress-induced abnormalities in hormone levels b) impaired cortical control as a result of stress-induced formation of aberrant neuronal connections, c) hyperactivation as a result of kindling, d) autonomic imbalance due to damage to either the excitation ventral segmental limbic system or to the inhibitory lateral segmental limbic system, e) above normal basal tone in both the sympathetic and the parasympathetic system due to limbic kindling, f) inappropriate hemispheric integration, g) inappropriate HPA-axis activation secondary to forebrain noradrenergic activity, h) inappropriate inhibition of GABAergic

activity due to high forebrain noradrenergic activity, i) increases in the CRH receptor expression in the locus coeruleus, j) increased CRH mRNA expression in the central nucleus of the amygdala, k) decreased benzodiazepine receptors in the amygdala, l) decreased benzodiazepine receptors in the locus coeruleus, m) increased CRH gene expression in the paraventricular nucleus, n) increased CRH gene expression in the amygdala, o) changes in serotonin activity and receptor expression due to variations in the CRH neurotransmission in the raphe nuclei and m) decreased glucocorticoid receptor expression in the hippocampus. Other interesting mechanisms, through which early life experiences can predispose to altered stress vulnerability and subsequently to disturbances in mind-body health in adulthood, were presented at the 4th World Congress on Stress, 2002 (117). Some of the more important facts presented on the effects of the environment on mental and physical health are summarised below.

- Stimulation of the basolateral amygdala CRH1/CRH2 receptors by urocortin leads to long-term anxiety-like behaviours and autonomic hyperreactivity. This is seen as a form of amygdalar plasticity involving NMDA-type glutamate receptors and calcium-calmodulin dependent kinase-II mediated intracellular changes – similar to long-term potentiation (118).
- As seen in Chapter 6, CRH pathways innervate the dorsal raphe nucleus (DRN). Adverse early life experiences can lead to CRH-induced augmentation of serotonin-dependent behaviour. Neonatal stress can, in addition, cause desensitisation of the 5-HT_{1A} receptor-mediated auto-inhibition, decreased sensitivity to 5-HT_{1A} mediated inhibition of forebrain serotonin-release, a decreased response to alpha-1-adrenergic excitatory input and increased vulnerability to psychiatric illness in adulthood (119).
- *In utero* exposure to increased glucocorticosteroids (maternal stress or glucocorticoid therapy) leads to HPA presensitisation that is linked to premature psychopathologies in aging (120).
- Repeated neonatal maternal separation leads to persistent changes in central nervous system gene expression (121). Alterations include clusters of gene expression changes in elements of DNA-RNA synthesis and repair, neuronal growth and adhesion, intracellular signalling cascades and glial cells. Examples

include upregulation of the genes for DNA methyltransferase and ZIC (a zinc finger protein gene) in the prefrontal cortex and hippocampus as well as upregulation of neural cahedrin, NCAM, BDNF, expression of PKC-alpha, the subunit of the G protein and MAP kinase 4K3 genes in the prefrontal cortex and hippocampus. This type of work is still in the early stages but indicates that early rearing experiences can induce long-term stress sensitivity or resistance in the offspring by changes in plasticity and intracellular signalling cascades.

- Repetitive pain during neonatal intensive medical care, especially in premature infants, alters neurobiological developments such as basal autonomic responses and arousal state. (122). This does not augur well for future behavioural functions such as attention, self-regulation and executive functions.
- In adult women with a history of childhood abuse, multiple regression analysis showed childhood trauma, in addition to stressful periods in adulthood to be the best predictor of high neurohormonal reactivity to laboratory stress tests or to pharmacological challenges. These abused women also showed high CSF CRH levels, structural hippocampal changes and high levels of pro-inflammatory cytokines (123). Hippocampal damage with resultant low negative feedback on the stress response as a form of presensitisation has been discussed before.
- An interesting related phenomenon is the dysregulation of CRH in the central nucleus of the amygdala and bed nucleus of the stria terminalis due to stress during neonatal life. These systems, in contrast to the PVN, are known to increase their CRH expression in response to high levels of glucocorticoids and are able to stimulate the expression in other brain regions. Their dysregulation is strongly linked to low cortisol-HPA-axis negative feedback and to conditions such as excessive shyness and fear in children, the development of anticipatory anxiety, melancholic depression, post-traumatic stress disorder and self-administration of psychotropic drugs (124).

The examples given above pointed predominantly to predisposition to hyperactivity of the CRH/HPA system. It is however known that hypoactivty may exist in conditions such as the chronic fatigue syndrome. Many of the behavioural changes, with hyper- as well as

hyposensitivity are similar to that of sickness behaviour and even depression. The mechanisms underlying predisposition to hypoactivity are still largely unknown but certain processes are slowly becoming clear, including the following.

- Long-term desensitation of the HPA-axis may occur as a result of a single exposure to an extremely severe (homotypic but not heterotypic) stressor. This appears to be mediated through PVN gene transcription and can be induced by emotional as well as by immunological events. (125). This may very well have a bearing on the low CRH/HPA-axis activity seen in chronic fatigue syndrome and other disorders associated with stress system hypoactivity.
- Evidence also exists that a blunted HPA-response may develop as a result of early painful experiences or as a result of chronic pain (126). The apparent similarities between the suppressed HPA activity in chronic fatigue syndrome and in fibromyalgia, and the similarities between their behavioural symptoms and reported cognitive decline are striking.
- Reduced arousal and suppressed behavioural responsiveness may be related to deficient brain noradrenergic activity due to depletion (127) of noradrenaline stores. Noradrenergic depletion and alteration of alpha-2 receptors as a result of earlier stress experiences have been discussed in Chapter 3.
- The effect of intra-uterine predisposition to abnormal HPA-reactivity in later life seems to be dependent on a number of factors including birth weight and the gestational age at which the subject is born and it is suggested that, depending on such factors, foetal programming of the HPA axis may result in either hyper- or hypoactivation of the stress axis (128).

The previous paragraphs dealt with predisposition to either hyperactive or hypoactive activity of the stress response systems. There must, however be factors intended to render the individual stress-resistant. It has already been shown that positive early life experiences will lead to a lower stress reactivity and increased HPA-axis feedback control in the adult. It is also known that nutrition and physical activity can play a role in the sensitivity of the stress response systems. There are, however, other factors, which

between these two systems can lead to stress-related disturbances (134). The just referred to CRH-2 system mediates the stress-coping responses during the recovery phase of stress. In this context the peptide stresscopin, as well as stresscopin-related peptides, which act as specific ligands for the CHR-2 receptor, have recently been identified in humans (135). These peptides may represent endogenous ligands for maintaining homeostasis after stress and could very well become another potential pathway for therapeutic manipulation of stress-related diseases. Pharmacological studies, based on CRH-1 and CRH-2 receptor interactions are underway in an attempt to develop drugs to counter dysregulations in the stress systems. There can be no doubt that psychotherapy and other positive interpersonal interactions, which augment self-perception, will also lead to improvements of such dysregulations. The effects of prenatal glucocorticoid programming of the brain corticosteroid receptors and the implications for coping and behaviour can be found in a paper by Welberg *et al*, 2001 (136). The foetal and neonatally induced hyperresponsiveness of the HPA, as discussed before, and the effects on adulthood coping responses (137) can naturally not be seen out of context with the receptor systems, but the complexity of such interactions are beyond the scope of this writing.

From work presented in this section and in previous chapters it is clear that early exposure to any environmental or immunological event that predisposes the individual to either hyper- or hyporesponsiveness of the main neuroendocrine systems could also predispose to future neurobehavioural and immunological abnormalities. Figure 7.1 can now be expanded to include these facts. This is seen in Figure 7.3 on the next page.

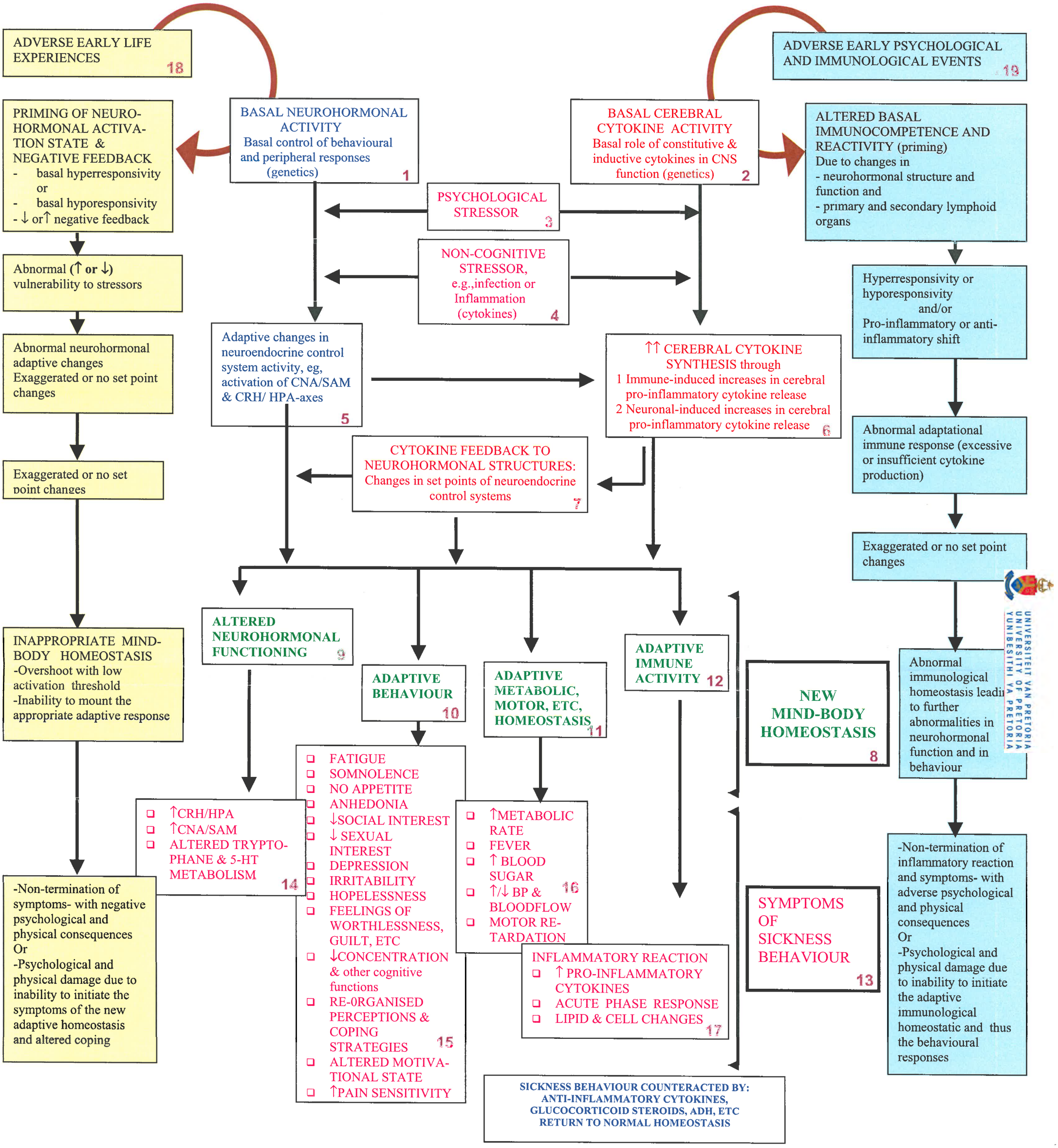

Figure 7.3: Sickness behaviour in psychoneuroimmunological context. Predisposition through early life experiences. [On the left of the diagram (18) it is shown that adverse life experiences can lead to hypo- or hyperreponsiveness of basal neurohormonal activity with subsequent abnormal stress vulnerability which may lead to an inappropriate adaptational homeostatic shifts and the potential for either non-termination of the symptoms of the adaptive homeostasis or an inability to mount the necessary new homeostasis. On the right of the diagram (19) it is shown that adverse psychological or immunological events can lead to altered basal immunocompetence and reactivity which upon subsequent challenges by stressors could give rise to abnormal adaptive immunological homeostasis with adverse effects on neurobehaviour funtion and the potential for non-termination or non-initiation of the symptoms of the adaptive stress response]

Legend to Figure 7.3

Figure 7.3: Sickness behaviour in psychoneuroimmunological context. Predisposition through early life experiences. [On the left of the diagram it is shown that adverse life experiences can lead to hypo- or hyperreponsiveness of basal neurohormonal activity with subsequent abnormal stress vulnerability, which may lead to an inappropriate adaptational homeostatic shift and the potential for either non-termination of the symptoms of the adaptive homeostasis or an inability to mount the necessary new homeostasis. On the right of the diagram it is shown that adverse psychological or immunological events can lead to altered basal immunocompetence and reactivity which, upon subsequent challenges by stressors, could give rise to abnormal adaptive immunological homeostasis with adverse effects on neurobehaviour function and the potential for non-termination or non-initiation of the symptoms of the adaptive stress response.]

Sickness behaviour was discussed in a previous section as a practical example of the psychoneuroimmunological interaction. Many of the symptoms of sickness behaviour correspond to that of certain mental disorders. It would therefore seem feasible to argue that continuation of the symptoms of sickness behaviour, after recovery from the physical disease, could give rise to mental abnormalities - especially in the person presensitised by genetic and early life experiences. This statement is presented later in this chapter as a hypothesis and its merits defended with appropriate examples. It almost speaks for itself that not only immune-related physical disease, but virtually any type of stressor that impacts on the neuroendocrine systems, could have the same effect. At this stage it becomes necessary to ask what mechanisms are involved in the termination of sickness behaviour and what could perhaps lead to failure to terminate the response with subsequent continuation of the symptoms.

7.3 Termination of the symptoms of sickness behaviour and failure to terminate the response.

Cortisol is probably the major feedback substance that not only suppresses the sickness behaviour-associated hyperactivity of the CRH/HPA axis, but also shifts the inflammatory response in an anti-inflammatory direction. The underlying mechanisms have been discussed in previous chapters and earlier in this chapter. The putative mechanisms through which the peripheral inflammatory response, as well as other potential psychological stressors can stimulate the CRH/HPA-axis have also been discussed. Through its negative feedback on the hippocampus, anterior pituitary and hypothalamus as well as its inhibition of the production of pro-inflammatory cytokines, cortisol can thus have a direct as well as an indirect suppressive effect on its own hypersecretion and on sickness behaviour in total. Factors that lead to cortisol resistance can thus by implication result in a continuation of the hyperactivity of the neuroendocrine systems, the pro-inflammatory activity, as well as the behavioural symptoms.

Several factors can contribute to cortisol resistance and therefore to continuation of sickness behaviour symptoms. One of these is a basal hyperactivity of the stress systems.

The predisposition to a hyperactive CRH/HPA-axis has been discussed in the previous section – with the major mechanisms being the down-regulation of hippocampal and upregulation of amygdalar glucocorticosteroid receptors and therefore a weaker negative feedback. It is obvious how such a predisposition can lead to the continuation of the sickness behaviour symptoms long after an immunological or psychological stressor has ceased to exist. It is also clear how the hyperactivity of the CRH/HPA, as well as the CNA/SAM-axis, can be further amplified by a negative emotional state which in itself can act as stressor and further propagate the symptoms characteristic of sickness behaviour, with the potential to develop stress-related disorders. It is perhaps at this stage necessary to recall that long-term depressive moods in themselves may lead to cortisol-induced atrophy of hippocampal neurons with subsequent lowering in the negative feedback system (138). The opposite is, however also true, i.e., that a positive psychological mood and a feeling of control may help to reduce the activation state of the neurological stress systems and thereby remove a strong stimulus for the production of intracerebral pro-inflammatory cytokines. These interactions were discussed in more detail in previous chapters.

Although glucocorticoid resistance is in the majority of cases a function of alterations in receptor expression, there are other reasons why it may be present, including some prereceptor (conversion of corticosterone to cortisol, plasma cortisol binding proteins) and some postreceptor mechanisms. Some of these have been referred to in previous sections and will not be discussed again. However, one mechanism very relevant to the contribution of cortisol resistance to the non-termination of the symptoms of sickness behaviour is the role of cytokines. Cortisol resistance due a suppressed negative feedback may be induced by the very same cytokines that form part of the sickness behaviour complex. Over 20 studies showed that cytokines, especially those involved in inflammatory conditions, could alter glucocorticoid receptor density and functioning. Some contradictions exist between the results of those studies using whole cell techniques and those using cytosolic radioligand binding (139). The overriding conclusion is, however, that pro-inflammatory cytokines can reduce the expression of glucocorticoid receptors as well as down-regulate their functioning (139). This would

naturally suppress the negative feedback on the HPA-axis and their effect on cytokine production, resulting in continued activation of the stress axes and augmentation of pro-inflammatory cytokine production. This can, via the cerebral cytokine relay system, further increase the activation state of the neuroendocrine stress axes - resulting in a type of positive feedback system that supports the continuation of the sickness behaviour with the potential to progress towards behavioural disturbances.

It should be mentioned that genetic abnormalities due to mutations in the glucocorticoid receptor gene is known to occur and that these receptor alterations generally appear to result in cortisol resistance (140). Genetic disturbances of the gene with glucocorticosteroid hypersensitivity and concurrent hypoactivity of the HPA-axis may exist. However, glucocorticoid receptor expression studies are not freely performed and such disturbances, if they exist, have not yet been reported.

Several substances, besides glucocorticosteroids, are involved in the control of pro-inflammatory activity, including the anti-inflammatory cytokines, ADH, α-melanocyte stimulating hormone, the SAM-axis and certain members of the interleukin-1 family (5,30,31). The molecular mechanisms involved in containment of the sickness response are sometimes referred to as the cryogens (32). The role of the glucocorticosteroids is generally that of normal negative feedback. The HPA-axis, as previously mentioned, is stimulated by pro-inflammatory cytokines. The glucocorticoids thus secreted can in turn control the cytokine-induced effects a) by down-regulation of pro-inflammatory cytokine synthesis and release through inhibition of transcriptional and post-transcriptional expression of the IL-1β gene and by decreasing the stability of the IL-1β mRNA, b) by decreasing the ratio of type I IL-1 to type II IL-1 receptors, and c) by suppressing the conversion of proIL-1β to its biological active form through inhibition of the IL-1β converting enzyme (30,34,35). ADH, a substance that acts in synergism with CRH, as shown in Chapter 5, is also involved. Fever-induced ADH has, for instance, been shown to limit the suppressive effect of IL-1β on the behavioural functions (33). Failure of any one of the factors involved in terminating the inflammatory process can contribute to the continuation of the sickness behaviour.

The interactions between the two main stress axes and cytokines, which are quite complicated, have been discussed in Chapters 4 and 5 and are for the sake of convenience summarised in Figure 7.4. As indicated in previous chapters, the two main stress neuroendocrine systems can be stimulated by pro-inflammatory cytokines and in turn can control these inflammatory mediators. Furthermore, both axes can influence as well as be influenced by the behavioural functions. It is, however, important to recall the effect of hyperactivation of the two main stress axes – as in the case of sickness behaviour – on the cytokine shift. In Figure 7.4 it is shown that both axes tend to shift the immune response away from cellular towards humoral immunity and the cytokine profile from a pro-inflammatory towards anti-inflammatory cytokine profile.

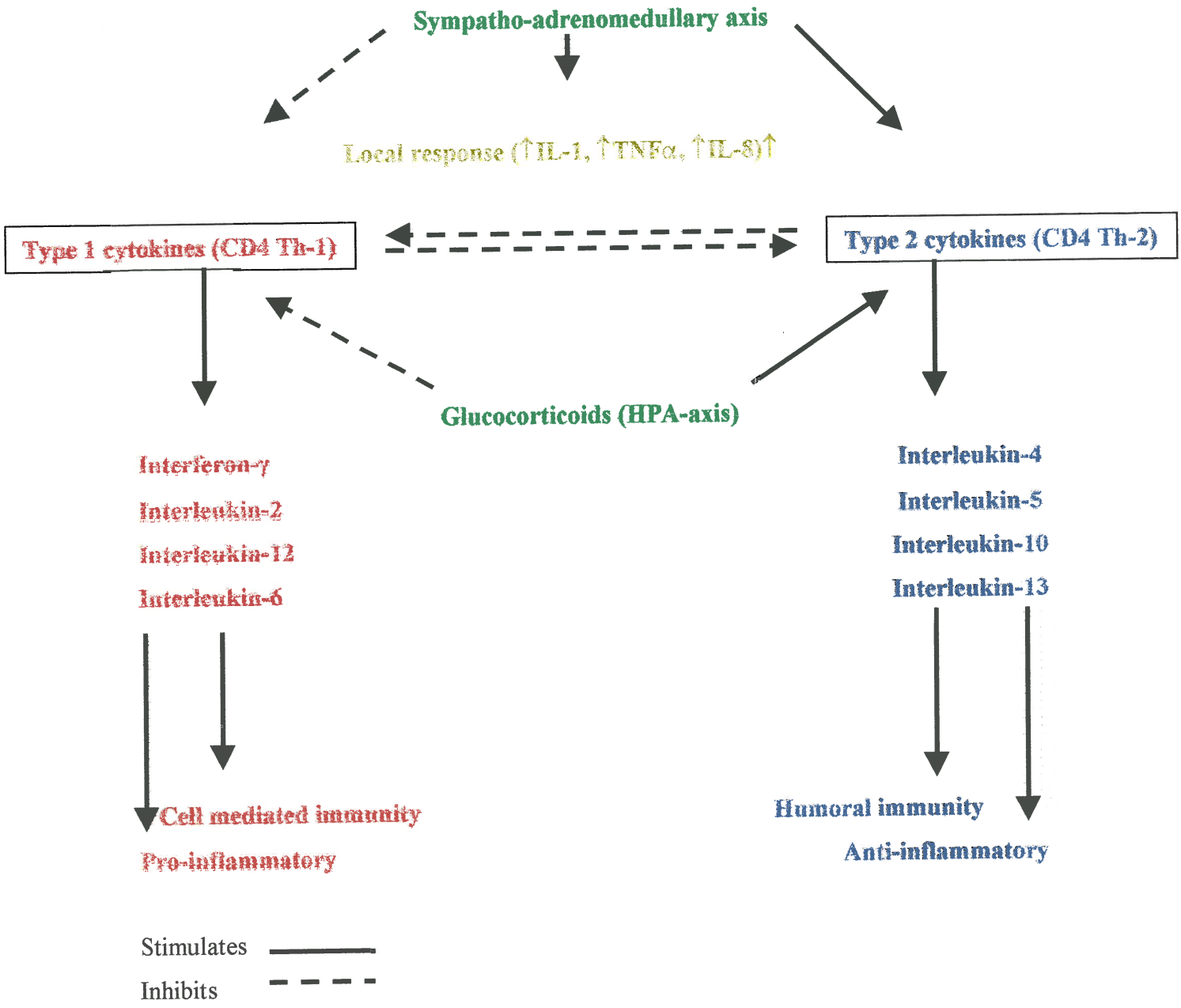

Figure 7.4: The interactions between the two main stress axes and cytokines. [Both the SAM-axis and the HPA-axis suppress the production of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines by switching CD4 cells from a Th-1 to a Th-2 pattern. They also inhibit production of IL-1 which acts as co-stimulator in T-cell activation]

It is highly possible that individuals who become resistant to the effects of the feedback mechanisms, either through psychological predisposition or through the combination of genetics and predisposition, and who subsequently, develop sickness behaviour may be at risk for non-termination of the sickness behavioural response and thus at risk for the development of physical or psychological disorders. Various factors, psychological, as well as physiological, could influence the eventual outcome. The following paragraphs are dedicated to providing the necessary information in order to support such a hypothesis.

7.4 The Hypothesis: Uncontrolled sickness behaviour may lead to any of a number of mental disturbances – partially dependent on predisposition by early life experiences.

Earlier in this chapter, the symptoms of sickness behaviour have been shown to represent a new adaptive homeostasis, which can be seen as a pattern of conscious and subconscious coping responses in the face of whatever the initiating stressor. We have further seen that many of the symptoms of sickness behaviour would appear to correspond to characteristics known to occur in certain mental disorders. These symptoms are largely the reflection of cytokine-induced neuroendocrine changes that include disturbances in the CRH/HPA-axis, the CNA/SAM–axis and the central serotonergic systems. Proof of the ability of cytokines to cause such neurobehavioural disturbances was demonstrated in Chapter 6 where it was shown that cytokines could induce disturbances ranging from mild constitutional symptoms (fatigue, chills, headaches, fever, etc) to serious psychiatric problems such as depression, delirium and psychosis. Examples of associations between classes of the DSM-IV and the inflammatory response were given in Chapter 2 and the links between disturbances of the neuroendocrine systems involved in sickness behaviour and a number of mental disturbances were touched upon in Chapters 3 and 5. Earlier in this chapter it was shown that the threshold for hyperactivation of these neuroendocrine systems could be lowered by early life experiences, and that resistance to the normal negative feedback mechanisms that terminate the hyperactivity of the neuroendocrine and immunological systems

involved in the symptoms of sickness behaviour can occur. It is therefore hypothesized that continuation of sickness behaviour after recovery from the initial stressor could form the basis of mental disturbances. This will be particularly relevant in individuals who are already vulnerable due to a genetic and psychological predisposition of the neuroendocrine and/or immune system. It is feasible to suspect that the type of disturbance likely to develop will be determined by the genetic disposition and the priming by early life experiences. It speaks for itself that psychological stress or a secondary inflammatory or infectious condition, even subclinical, would contribute to the psychiatric disturbance and even exacerbate the condition with dire consequences for mental health. The potential consequences for physical health are equally alarming and many physical disorders are presently known to be associated with stress-related disturbances of the HPA-axis. These physical disorders, although most of them now known to be associated with very specific behavioural characteristics, will largely be ignored. However, some of them will be referred to under mental disturbances due to general medical conditions.

7.4.1 Mental disorders as a continuation of sickness behaviour

In this section the similarities between sickness behaviour and a number of mental disorders are briefly discussed in support of the proposed hypothesis. The suggestion made in Chapter 2, i.e., that inflammatory processes of the brain may be a factor in a number of behavioural disturbances, will be elaborated upon and the role of antidepressants will be touched upon. Although a number of disturbances will be looked at, major depression will be the prime focus. It has to be stressed that the immunological involvement to be described is in no way suggested to replace other factors as the cause of whatever mental disturbance is discussed.

For quite a while, there have been indications that the immune system may play a role in the etiology of depressive moods, specifically in the etiology of major depression. In Chapter 2, reference was made to earlier publications showing the connection between abnormal immune functioning and mood disorders. The first major milestone in the development of the hypothesis that immune changes may underlie the etiology of major depression was the macrophage theory of depression by Smith in 1991 (141). Due

partially to the fact that immunology is still a developing field, immune suppression was initially thought to be a characteristic of major depression. We now know that it is merely a shift in immune function. The second major milestone was the interleukin hypothesis of major depression as described by Maes in 1995 (142). At present, it is fairly well accepted that depression is more often than not accompanied by a pro-inflammatory/Th-1 shift in immune functioning. There are, however, still many unexplained aspects and much more interdisciplinary research is needed. As the purpose of this last part of the thesis is to show that unbridled continuation of sickness behaviour can give rise to several behavioural and even psyciatric disturbances, the next couple of paragraphs will deal with the similarities between sickness behaviour and the mood disorders. It will also be shown why the major depressive disorder is sometimes described as a central nervous system inflammatory condition. Sickness behaviour and depression will be compared in terms of behavioural characteristics, neurohormonal shifts and immunological patterns.

Previously in this chapter, sickness behaviour was shown to represent a cerebral activation state where subsequent cytokine-induced neurohormonal changes can lead to a wide spectrum of behavioural changes. The similarities between the psychiatric symptoms of the mood disorders and the symptoms of sickness behaviour are striking. As previously seen, the differences in sickness behaviour symptoms vary with the severity and duration of the condition from flu-like constitutional symptoms to anhedonia to severe cognitive disturbances. It is tempting to speculate that this, except for the duration, may partially be reflected in the differences between the major depressive disorder and the dysthymic disorder. In comparing the list of symptoms (depressed mood most of the day; nearly every day; markedly diminished interest or pleasure in almost all activities; decreased appetite or weight loss, hypersomnia or insomnia nearly every day; psychomotor retardation or agitation nearly every day; fatigue or loss of energy nearly every day; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate and recurrent thoughts of death, suicidal ideation or a suicide attempt) from which at least 5 have to be present to represent a major depressive episode (143), it is clear that they all fall within the scope of the behavioural symptoms (fatigue, somnolence, no appetite, anhedonia, loss of social and sexual interest,

depressive moods, irritability, feelings of hopelessness, worthlessness, guilt, a lack of concentration, and a decline in other cognitive functions, reorganised perceptions and coping strategies as well as altered motivational states) that may form part of sickness behaviour.

For as far as we are able to come to any dogmatic conclusions, there is a good correspondence between the basic neuroendocrine perturbations of sickness behaviour and major depressive disorders. Abnormalities of the CRH/HPA system with dysfunctions in the thyroid axis, as well as in noradrenaline and serotonin metabolism and receptor function are, as for sickness behaviour, known to be present in depression. Although most biological models of major depression describe CRH/HPA-axis hyperactivity as the norm, preliminary indications are that other patterns may also exist. There is some evidence for hypercortisolaemia to predominate in typical depression and hypocortisolaemia in atypical depression. Significant improvement has, in fact, been seen with prednisone augmentation of antidepressant therapy in treatment-resistant depressive patients with hypocortisolaemia and severe fatigue (144). Depression with severe fatigue and hypocortisolaemia obviously puts a very fine dividing line between depression and the so-called chronic fatigue syndrome.

The hypersecretory state of the HPA-axis of major depression is, as for sickness behaviour ascribed to hypersecretion of CRH due to, amongst other things, a suppression in the negative feedback mechanism – both exhibiting non-suppression of cortisol secretion upon dexamethasone administration. The degree of non-suppression would appear to correlate with the levels of IL-1β, both in depression and sickness behaviour. This is in agreement with findings that immune challenges could decrease the affinity of the corticosteroid receptors involved in the negative feedback of the HPA-axis (145). It is also known, as described in Chapter 6, that immune challenge-induced pro-inflammatory cytokine production could stimulate CRH activity and thus cause hyperactivity of the CRH/HPA system. Immunological activity, as seen in sickness behaviour can thus increase CRH activity both by stimulating the secretion directly and by inhibiting the negative feedback. Major depression is similarly associated by a central CRH drive as

represented by above normal CRH levels in the cerebrospinal fluid, increased CRH mRNA levels in the paraventricular nucleus and reduced CRH receptor density in the frontal cortex (146). This central CRH drive which is supposed to be of short duration during sickness behaviour and which is present in a more chronic form with major depression, is said to act as compensatory mechanism against the effects of the elevated cortisol levels on immune function. This may, however, be a potentially dangerous situation in conditions of glucocorticoid receptor downregulation where the glucocorticoid suppression of pro-inflammatory cytokines is reduced. Such a condition of pro-inflammatory stimulation by CRH (see Chapter 5 for details on the effects of CRH on the immune system) and downregulation of the cortisol anti-inflammatory activity may lead to unbridled continuation of sickness behaviour, or in the case of individuals with trauma or serious infections to the systemic inflammatory response syndrome, septic shock, or even multiple organ failure. In case of the first possibility, i.e., non-termination of sickness behaviour, it is highly feasible to expect that the symptoms would reflect that of major depression. In fact, that it could indeed be a case of sickness behaviour that developed into a chronic state of depression. Previously in this chapter, it was shown that priming of the CRH/HPA-axis by adverse early life experiences can predispose to above normal basal activity of the system. It is clear how such predisposition would lower the activation threshold and could render the individual vulnerable to non-termination and a switch from appropriate sickness behaviour to a dysfunctional major depressive state.

The main disturbance of the thyroid axis in major depression would appear to be suppression of TSH secretion (147). Such TSH suppression during HPA-axis hyperactivity is to be expected and does not require any explanation. In fact, if other endocrine systems controlled through hypothalamic liberins and statins are to be investigated the same pattern would most probably be found with regard to the tropic hormones. Sickness behaviour in the acute situation is, in contrast, accompanied by a hypermetabolic state. However, should sickness behaviour progress into a more chronic condition the hyperactive CRH/HPA-axis would lead to suppression of the thyroid axis – similar to that found in depression. The reason for this is that TSH is, in the case of hyperactivity of the CRH/HPA-axis, suppressed not only directly by above normal

cortisol levels but also indirectly through a CRH-stimulated increase in somatostatin that in turn inhibits TSH release (148). Not to be discussed here, but of interest with regard to the similarities between prolonged sickness behaviour and major depression, is the fact that hyperactivity of the CRH/HPA-axis can have similar suppressive effects on the reproductive axis and the growth axis (148).

The serotonin abnormalities associated with mood disorders (149) would appear to include

- central nervous system changes in presynaptic serotonergic neurons due to a deficiency in L-tryptophan availability
- compensatory increases in post-synaptic receptor density, affinity and responsiveness of 5-HT2 receptors
- down-regulated/desensitized post-synaptic 5-HT1A receptors.

A similar decrease in tryptophan availability has been described earlier in this chapter under the discussion of the neurological characteristics of sickness behaviour (14). This decrease in tryptophan deficiency of sickness behaviour, as previously discussed, results from a cytokine-induced shift to the kynurenine pathway. At this stage it would be risky to venture into an in depth comparison between the alterations in serotonin metabolism as it is becoming clear that the various cerebral areas undergo different changes in their serotonin metabolism and receptor activity – both during immunologically induced sickness behaviour and with major depression (146).

If sickness behaviour can evolve into mood disorders such as major depression or the dysthymic disorder it should in theory be possible that the factors responsible for the neurological disturbances of sickness behaviour should also be able to lead to the neurological disturbances of depression. In previous paragraphs and in Chapter 6 it was shown that cytokines can give rise to the total spectrum of behavioural and physiological changes seen in sickness behaviour, either directly or through cytokine-induced changes in neuroendocrine function. It has also been shown that the whole mechanistic cascade of sickness behaviour can be initiated by an initial non-cognitive stressor such as infection, inflammation or trauma, or by stress-induced neurological activity. We have furthermore

seen how the neurological stress systems can be activated by pro-inflammatory cytokines as the result of the impact of a non-cognitive stressor. Two questions thus apply, i.e., whether any correspondence exists between the immune response of sickness behaviour and that of the mood disorders and whether the pro-inflammatory immune pattern of sickness behaviour can be causally related to the neurological changes known to occur in mood disorders such as major depression. The first question will be dealt with in subsequent paragraphs. The second has, to a large extent been answered in previous sections and can be conceptualized by saying that

- Hyperactivity of the HPA-axis can be induced by IL-1 and IL-6 in cooperation with other cytokines, by inflammatory-related changes in noradrenaline and serotonin turnover, and by any factor that causes a downregulation of the negative feedback of the HPA-axis. With regard to the latter, we should recall that IL-1 can for instance downregulate glucocorticoid receptor expression or the translocation of the receptor from the cytoplasma to the nucleus. Not to be discussed here, but of importance for a more in depth understanding, are the roles and interactions of cytokines, eicosanoids and glucocorticoids in the activation of the HPA-axis by immune onslaughts. This can be found in a review by Buckingham *et al,* 1996 (150).
- Noradrenergic hyperactivity can be induced by cytokines, either directly, or as a result of the control of the CRH/HPA-axis over the system (Chapter 5), and the positive reverberating influence between the two stress axes (Chapter 3).
- Central serotonin is also known to be influenced by the pro-inflammatory reaction seen in sickness behaviour. Pro-inflammatory cytokines such as IL-1β, IFNγ and TNFα have, for instance, been shown a) to alter extracellular serotonin (5HT) levels in the hypothalamus, the hippocampus and the cortex, b) to modulate the activity of the serotonin transporter involved in central serotonergic neurotransmission by serotonin re-uptake, and c) to induce the activity of the first enzyme of the kynurenine pathway (indoleamine-2,3-dioxygenase) that converts tryptophan to kynurenic acid and quinolinic acid with a resultant tryptophan-depletion and/or reduction in the tryptophan:competing amino acid ratio with the potential for a reduced serotonin production [Reviewed by Maes, 1999 (151)].

- The downregulation of the thyroid axis can happen secondary to an upregulation of the HPA-axis and is therefore hardly necessary to discuss. Yet, there are indications that the depression-associated alterations of the thyroid axis can also be induced by inflammatory activity – whether this is indeed a direct effect or not is not always clear. What is known is that low basal TSH and abnormal T3 and T4 levels are present in the majority of physical diseases where activation of the inflammatory response happens to be a feature and that IL-1β and IL-6 are involved in inflammatory-related thyroid axis suppression (152,153).

To return to the first question. The immunological alterations described in, for instance, major depression follow virtually an identical pattern to that known to occur in sickness behaviour. These similarities were first pointed out by Maes in 1995 in his interleukin hypothesis of depression (142), and are well reviewed in a more recent paper (151). The reader is referred to his paper for references to the original authors. In the latter publication, Maes, 1999 (151), presented the evidence for the existence of an inflammatory response, similar to the response known to occur with physical diseases, in major depression by subdividing the supporting evidence into direct and indirect indicators of the inflammatory response. Direct evidence for the presence of a inflammatory response in mood disorders comprises findings such as increases in circulating monocytes and neutrophils, increased neopterin and prostaglandin levels, activation of the acute phase response (with increases in positive acute phase proteins and decreases in negative acute phase proteins), and increases in pro-inflammatory cytokines such as IL-1β, IL-6 and IFNγ. Indirect evidence, generally used in clinical diagnosis for the detection of the inflammatory response include a decreases in serum zinc and serum iron levels, alterations in lipid metabolism with a typical inflammatory response pattern of, amongst other, an increased C20:4ω6/C20:5ω3 ratio, and erythropoeitic changes typical for the systemic inflammatory response, including hypoferraemia in the presence of tissue iron overload. Evidence for the presence of such inflammatory response markers has repeatedly been shown in subsets of patients with major depression (151). In addition, the presence of membrane lipid abnormalities, typical for inflammatory conditions, are current major points of interest in psychiatry, including depression - with the focus on dietary supplementations for the correction of the C20:5ω3 component

(154). Of interest is the fact that most of the above discussed changes can be induced by the same pro-inflammatory cytokines responsible for the neurobehavioural symptoms of sickness behaviour. The fact that psychological stressors can induce a pattern of pro-inflammatory cytokine hypersecretion and a polyunsaturated fatty acid profile similar to the inflammatory response of sickness behaviour (155) once again demonstrates the similarities between the so-called psychological and the so-called medical disturbances.

The discussion above confirmed the presence of an inflammatory response in mood disorders such as major depression. In fact, depression has recently been described as a state of cerebral inflammation. This is a vast oversimplification. The question that comes to mind is whether the idea of major depression as pro-inflammatory response presents a new independent hypothesis on the etiology of depression and whether some of the neuroendocrine-based or psychologically based theories are rendered obsolete by the inflammatory approach. The answer to both would be an emphatic no. It can rather be said that the inflammatory response represents a major component of mood disorders that had previously been overlooked. These interactions between the neuroendocrine changes and behaviour, between behaviour and cytokines and between the neuroendocrine functions and cytokines have all been discussed. The introduction of the cerebral inflammatory response, influenced by, as well as influencing the neuroendocrine-behavioural functions, explains the connection between peripheral infectious and inflammatory events and the behavioural functions, as well as between psychologically induced predisposition to, and exacerbation of physical diseases. It would appear to form the core of the psychoneuroimmunological interaction. This does indeed deprecate any dogma that approaches mind and body as two separate entities.

It is at this stage relevant to refer back to the biopsychosocial approach. The psychoneuroimunological approach as described above can now be applied to the multiple entry point concept as suggested by the biopsychosocial approach to disease – including mental disorders as it becomes virtually impossible to separate mental from physical disease. It is obvious that the stimulatory input can be at, and the effector output from, virtually any point in the behavioural, neuroendocrine or immunological spectra.

The time the effects are presented would further not necessarily have to correspond to that of the primary stimulus as presensitisation during early childhood, or even later, may find behavioural expression only in the event of a trigger situation. The psychoneuroimmunological alterations characteristic of sickness behaviour can serve both as presensitisation factors and as trigger situations. It is at this stage perhaps necessary to recall that the primary stimulus for presensitisation may occur as early as prenatal life. Examples of such influences were discussed in Chapters 3 and 4 and earlier in this chapter. Of specific relevance to this writing is the fact that cytokines are of significant importance during the development of the central nervous system where they are involved in processes such as neuronal development, synaptogenesis, regeneration and plasticity, and that over- or underproduction of cytokines may alter the development of the central nervous system (156).

To clearly demonstrate the totality of the mind-body interaction in terms of the CRH/HPA-axis it would be necessary to do a comparative review on all mental and physical disorders associated with alterations in each system and to note both the physical and mental changes in all of them. This would no doubt result in startling simplification and facilitation of a proper understanding of what at present involves a wide spectrum of psychological and physical conditions. Such a writing is, however beyond the scope of this thesis.

The brief for this section was to show the correspondence between sickness behaviour and mood disorders – particularly major depression. Having demonstrated the similarities in terms of symptomatology, neuroendocrine changes and immune status, and knowing that earlier life events may predispose to a lowered triggering threshold, as well as to termination-failure, it should perhaps be asked whether depression and sickness behaviour are not one and the same thing. This, in fact, has been suggested by the malaise theory of depression (157). The essence of the malaise theory of depression is that it proposes the state or emotion of malaise to be considered the core symptom of depression, rather than the sadness or mood. On this basis, the primary pathology of depressive disorder is suggested to be somatic with the variable mood changes secondary

responses to the physical disorder. This, on first glance would appear to make sense. However, to see depression as sickness behaviour is to equate the stress response, which represents a transient adaptive new homeostasis or coping mechanism, with stress pathology. The malaise theory further suggests that many antidepressants exert their antidepressant action primarily by alleviating the physical state of malaise – with improvement of the behavioural aspects as secondary gain. This concept would appear to contain some truth with strong empirical evidence for analgesic effects of tricyclic antidepressants and some support for the assumption that non-tricyclic antidepressants may also have analgesic properties (157,158,159,160). Perhaps more relevant to the similarities between the inappropriate continuation of sickness behaviour and major depressive disorder is the fact that certain antidepressants would appear to have anti-inflammatory effects mediated partially through suppression of the secretion of pro-inflammatory cytokines. Antidepressants have indeed been reported to successfully control the immune reactivity and cytokine responses in depressed patients (145). One example of the anti-inflammatory effects of cytokines is the selective phosphodiesterase inhibitor Rolipram that was shown to suppress the production of cytokines such as TNF-alpha and interferon-gamma (161). There are, however, indications that certain anti-inflammatory effects may be mediated primarily through the influence on neurotransmitters such as serotonin. Selective serotonin reuptake inhibitors have, for instance been shown to suppress the secretion of acute phase proteins, as well as IL-6 levels. (161). Results from different laboratories on the anti-inflammatory effects of the different antidepressants are, however, not always in agreement and could at present not summarily be used to rationalize such therapeutical applications of antidepressants (145,161). One aspect of antidepressants that is apparently never considered when examining the presumed anti-inflammatory effects is that such effects may indirectly be mediated via the influence on the CRH-producing neurons. There are for instance strong indications that antidepressants such as fluoxetine, phenelzine and idazoxan can reduce CRH synthesis in the paraventricular nucleus and that it can improve glucocorticoid receptor binding (162). The potential anti-inflammatory effect, i.e., suppression of the production of a potentially pro-inflammatory substance such as CRH (Chapter5), as well as an antidepressant effect through normalisation of the CRH/HPA-axis is obvious.

Having demonstrated how a functionally adaptive state such as sickness behaviour can give rise to a psychopathological condition such as major depression, and probably also to the dysthymic disorder, we will now briefly turn to depression due to a general medical condition.

The prevalence of depression due to a general medical condition is vastly underestimated as can be seen from statistics which show that at least 74 percent of men committing suicide during periods of major depression were, at that stage, treated for some or other medical condition (163). Although the incidence of depression was, a couple of years ago, said to be around 40 percent in the seriously physical ill, this can be assumed to be a significant underestimation as many ill individuals will not admit to, or may perhaps not even be aware of, the fact that they are depressed (164,165).

It has previously been shown that a variety of factors can lead to the typical neuroimmunological profile of sickness behaviour, which comprises activation of the inflammatory response accompanied by alterations in the CRH/HPA- and CNA/SAM-axis, as well as in central serotonergic activity. A host of medical conditions can cause such disturbances including almost all acute infectious and inflammatory afflictions, the majority of chronic infectious and chronic inflammatory conditions, as well as trauma and surgery – in fact virtually any form of tissue injury. Furthermore, as seen in Chapter 6, these symptoms can also be caused by certain medications. Under such circumstances one would then also find behavioural adaptations as occur in sickness behaviour or major depression, with symptoms such as depressive mood states, anhedonia, fatigue, suppressed appetite, disturbed sleeping patterns, psychomotor retardation, reduced interest in the environment and in ported social activities, altered pain perception and sometimes impaired cognitive abilities (145). Amongst the non-infectious medical conditions where hyperactivation and secretion of cytokines have been reported with the highest incidence are various autoimmune diseases, allergies, multiple sclerosis, rheumatoid arthritis, stroke, trauma, the premenstrual syndrome, post-partum depression and neurodegenerative disorders (145).

The question that should be answered is whether depression due to a general medical conditions is not merely a psychological reaction to the disability, pain and loss of functionality, and whether it does indeed form part of the new homeostasis of sickness behaviour. Empirical evidence suggests that the depression and several other cognitive symptoms found in such conditions are causally related to pro-inflammatory activity rather than mere expressions of psychological reactions to the medical condition (145). There can be no doubt that a reactive depressive mood could develop in many individuals in response to a disabling medical condition. However, sickness behaviour, which can result from a wide spectrum of stimuli, can without doubt exacerbate such a reactive depression, or even be the major cause of the depression associated with a general medical condition. Evidence that depression due to a general medical condition is more often than not related to the immune activation of sickness behaviour can be derived from the fact that the depressive mood associated with influenza can appear even in the absence of the clinical symptoms (166), that the depressive moods of recurrent herpes infections may precede the clinical manifestations (167), and that the development of depression in multiple sclerosis often precedes the neurological diagnosis or knowledge of the condition (168). Should, as just shown, sickness behaviour in the medically ill give rise to cytokine-induced depressive moods, it stands to reason that it could, just as previously described for the development of sickness behaviour into major depression or dysthymic disorder, give rise to major depression. In addition to the other factors, which could underlie the non-termination of sickness behaviour, reactive depressive moods resulting from the disability could contribute to the inappropriate continuation of the symptoms.

It has previously been argued that major depression may develop from the inappropriate continuation of sickness behaviour due to non-termination after recovery from the initiating physical disturbance. It was further suggested that such a depression could no more be seen as sickness behaviour but, should it fulfill the criteria for major depression or dysthymic disorder, be considered as such. In the case of depression due to a medical condition this argument falls away. As long as the causative medical condition is present the symptoms should indeed be seen as the adaptive sickness behavioural response,

intended to favour coping with, and recovery from, the primary physical disorder. It should, however, be remembered that both glucocorticoids and pro-inflammatory cytokines can, if the condition persists for too long, bring about a situation of non-termination – especially in those individuals predisposed to it through genetics and early life experiences. Non-termination as a result of glucocorticoid resistance, brought about by high glucocorticoid and anti-inflammatory cytokine levels, as well as by several other mechanisms, has previously been discussed. It is, however, also known that a decrease in other factors which contribute to the termination of sickness behaviour, such as the Clara cell 16kD protein (CC16), a natural anti-inflammatory secretory protein involved in modulating the cytokine network and its effectors (169), as well as other substances such as alpha-MSH and the anti-inflammatory cytokines mentioned before, may contribute to non-termination. A decrease in these anti-inflammatory mediators is known to occur in melancholic depression (145). The condition of resistance to termination can furthermore be exacerbated or prolonged by negative perceptions, feelings of no control or the inability to cope – in fact, by any factor that causes psychological stress (170). Should the individual experience such emotions in reaction to the disabling effect of the illness, or for whatever other reason, it could further exacerbate and prolong the sickness behaviour-induced behavioural disturbance. It is thus clear that, although the depression often found in association with medical conditions may be the expression of sickness behaviour, it does present with the possibility to develop into a chronic mood disorder – especially in individuals predisposed to it by their genetic make up and early life experiences.

In addition to be the stimulus for the expression of mood disorders, sickness behaviour may also – at least in theory - serve as the trigger for the development of other mental disorders to which the individual is predisposed. Instead of discussing the supporting details for the various mental disorders, the rationale on which the last statement is based will be presented, e.g., the fact that pro-inflammatory conditions are present in a variety of mental disorders, that pro-inflammatory cytokines could underlie the symptoms and that the pro-inflammatory cytokines can lead to the type of cerebral neurotransmitter alterations associated with a wide spectrum of psychiatric disturbances.

In Chapter 2 it was shown that immune alterations can be found in all categories of the DSM-IV. More important, it was shown that specific patterns of immunological alterations do not seem to be correlates of specific mental conditions. Not only are there strong similarities between the immune disturbances of various categories of mental disturbances, but also between that of mental disturbances and a host of physical syndromes. Examples of other mental disorders and syndromes where shifts in pro-inflammatory activity have been reported include delirium, dementia and other cognitive disorders (e.g., Alzheimer's disease, Creutzfeldt-Jacobs disease, Parkinson's disease, the neuropsychiatric symptoms of HIV/AIDS), mental disorders due to a general medical condition (e.g., autoimmune disorders, chronic inflammatory conditions, etc), schizophrenia and other psychotic disorders, certain anxiety disorders, dissociative experiences and disorders, eating disorders, sleep disturbances and disorders, as well as personality disorders and others (Chapter 2).

In referring back to Chapter 6, it is obvious that, at least in theory, all of the behavioural symptoms of the above disorders can potentially result from abnormal cerebral cytokine homeostasis. Examples of the possible effects of cytokines on behaviour include all the symptoms of sickness behaviour and major depression, as well as emotional instability, crying spells, agitation, irritability, overreaction to problems and frustrations, cognitive impairment, hallucinations, delirium, delusional ideation, amnesia, clouding of consciousness, disorientation, personality changes, seizures, coma, increased sensitivity to and inability to cope with pain, Parkinson's like symptoms and many others. The reader is referred to Chapter 6 for the roles of the various cytokines in these and other processes – as well as for the appropriate references.

The majority of mental disorders are associated with some form of alteration in central nervous system function or even structure. It can also with a fair amount of certainty be assumed that the behavioural effects of pro-inflammatory cytokines are largely mediated through their effects on the neurotransmitter systems of the CNS - and to a lesser extent, as in the case of certain types of pain, on the peripheral nervous system. Many of these cytokine effects on cerebral neurotransmission are indeed known, but we are still far from

understanding the influence of the synergistic interaction between the various cytokines on cerebral structure and function. The stimulatory effects of cytokines on the CRH/HPA-axis have been discussed in the last couple of paragraphs of Chapter 6. A more in depth account on the effects of cytokines on the CRH/HPA-axis can, however, be found in a review by Buckingham et al, 1996 (150). Amongst the other effects of individual cytokines which could have a bearing on psychopathology (161) are the facts that a) IL-1, with high receptor density in the hippocampus, hypothalamus and brain stem, stimulates the release of peripheral catecholamines as well as brain stem and hypothalamic noradrenaline, and increases the turnover of noradrenaline, serotonin, tryptophan and dopamine in the brain, b) IL-2, with high receptor density in the locus coeruleus and pyramidal cell layer of the hippocampus, stimulates dopaminergic neurotransmission - particularly dopaminergic metabolism in the prefrontal cortex and may exert an effect on motor function by regulating striatal dopaminergic functions. It also increases hippocampal noradrenergic metabolism and may have a sedative effect through its influence on the locus coeruleus and nucleus caudatus. It has further been shown to inhibit acetylcholine release in the hippocampus and frontal cortex and may lead to neuronal loss and degenerative changes in the hippocampus with loss of mnestic functions, c) IL-6, with its high receptor density in the hippocampus and prefrontal cortex, stimulates the secretion of dopamine and noradrenaline and increases dopamine and serotonin turnover in the hippocampus and prefrontal cortex, d) TNF-alpha would appear to have a biphasic influence with stimulatory effects on the catecholaminergic systems in the acute situation and suppressive effects upon chronic exposure. It has further been implicated in cytotoxicity and demyelinisation. Most of the above effects reflect that of single cytokines in the acute situation.

In the previous paragraphs the fact that the inflammatory response is present in a variety of mental disorders, that psychiatric symptoms associated with a variety of mental disorders could result from an increase in pro-inflammatory cytokines, and that the inflammatory cytokines could underlie alterations in neurotransmitter systems, were discussed. The potential implications are clear, i.e., that, depending on the genetic predisposition and priming by previous life experiences, the cerebral inflammatory

response that underlies sickness behaviour may be the trigger for expression of any of a number of mental disorders.

An interesting phenomenon that once again supports the assumption of a central role for the CRH/HPA-axis in integrated mind-body homeostasis, is that many of these disorders are associated with abnormal functioning of the axis. Hyperactivity of the CRH/HPA-axis would appear to be present in the majority of the stress-related disorders in which the status of the axis has been investigated. The ostensible contradiction between non-termination of the inflammatory response and hyperactivity of the HPA-axis has been explained earlier in this chapter based on evidence from a wide spectrum of empirical research results. In short, mental disturbances or pathophysiological conditions as a result of non-termination of the inflammatory response and the neurohormonal disturbances associated with sickness behaviour will develop only when the individual has become resistant to the actions of the natural anti-inflammatory mechanisms – including cortisol. It is at this point important to remember that additional psychological stress during the appropriate period of sickness behaviour, can contribute to the inappropriate continuation of the condition.

The previous paragraphs dealt with the possibility of sickness behaviour developing into mental disorders known to be characterized by a hyperactivity of the CRH/HPA-axis and a pro-inflammatory shift in the cytokine balance. It was shown that early life adverse experiences may predispose the individual to such a transition through, amongst others, suppression of normal negative feedback and by increasing the baseline activity of the CRH/HPA-axis. However, it is also known that early life experiences may predispose to hypoactivity of the CRH/HPA-axis. A fact that, at first glance, would appear to directly predispose to inappropriate continuation of the inflammatory response. In contrast to the predisposition to hyperactivity of the CRH/HPA-axis with its relative resistance to negative feedback and subsequent continuation of the cerebral inflammatory response, our knowledge on the physiological aspects of those mental disorders where hypoactivity of the axis has been reported is rather scant and results often contradictory. The next couple of paragraphs will briefly look at conditions in which hypoactivity of the

CRH/HPA-axis has been reported, as well as the level of the CRH/HPA-axis where the insufficiency of the axis occurs and consider the possibility of sickness behaviour being the trigger for their induction.

Hypocortisolaemia, often accompanied by baseline sympathetic hypofunction and low serum serotonin and L-tryptophan levels, is reported for subsets of patients with the post-traumatic stress syndrome, fibromyalgia (FM), chronic fatigue syndrome (CFS), chemical intolerance and other stress related somatic disorders (171,172,173).

At this point in time the inconsistency in results confounds absolute conclusions. Amongst the disorders where HPA-axis hypoactivity can occur, PTSD differs from the others, not only in its etiology, but also at the level where the suppression occurs. PSTD is a typical severe stress-related disturbance, classified according to the DSM-IV as an anxiety disorder (174). In contrast to many other stressor-induced disorders, the precipitating traumatic event can usually be precisely identified, and re-experiencing of the event constitutes a major contribution to non-extinction and exacerbation of the allostatic load. Early life experience, genetics and support systems are bound to play a role in the development and progression as distinct differences exist between the psychological symptoms and neurological profiles of patients. Low cortisol levels have for instance been reported for combat-related PTSD (175), in PTSD-diagnosed women with a history of childhood sexual abuse (176), adolescents after an earthquake (177), and in other subsets of PTSD patients. However, there have been reports of normal and occasionally even high levels of cortisol in PTSD patients. A possible explanation comes from the fact that the activity of the HPA-axis in PTSD may change over time, depending on the psychiatric symptoms (178). It is thus essential that future research takes in consideration the stage as well as the symptoms. The best current conclusion on the CRH/HPA-axis disturbance in PTSD would appear to be that of Ehlert and Heinrichs, 2001, (173), i.e., that PTSD is associated with alterations of the axis that can be interpreted as a latent hypocortisolism with an increase in the feedback inhibition to the pituitary and the adrenals, while neuronal CRH release appears to be above normal. Of interest, and as could be expected, the elevated CRH is often accompanied by elevated

basal CSF noradrenaline levels. (162) It has been proposed that in PTSD patients with low cortisol levels the stress response is maladaptive rather than adaptive and that the reasons may be found in a combination of genetics and perinatal as well as childhood and adolescent stress (179,180) – a situation that could naturally influence the coping mechanism and the degree of control experienced by the individual. PTSD patients with low cortisol correspond to patients with melancholic depression in the fact that both groups demonstrate central hypersecretion of CRH, and differ in the fact that melancholic depression is characterized by hypercortisolaemia, in contrast to PTSD where hypocortisolaemia can be present. It is tempting to speculate that the relative adrenal insufficiency in PTSD could represent adrenal burn-out due to uncontrolled stress-induced stimulation during the earlier stages, and that the hypersecretion of CRH could partially be the result of cortisol-induced hippocampal damage at the stage of trauma or during the initial stages of development of PTSD – which would naturally present as a CRH oversecretion. A degree of hippocampal atrophy has indeed been observed in combat veterans with PTSD (181). However, the influence of CRH neurons in the prefrontal cortex and central nucleus of the amygdala as possible contributors should not be ignored.

In addition to PTSD low cortisol levels have also been reported in somatoform disorders and related syndromes[1]. According to the DSM-IV definition (182), somatoform disorders can be defined as the presence of physical symptoms that suggest a general medical condition but are not fully explained by a medical condition, by the direct effects of a substance or by another medical disorder. Idiopathic pain and gastrointestinal disturbances form important aspects, not only of several of the somatoform disorders, but

[1] No distinction will be made between somatoform disorders and either fibromyalgia or CFS – despite differences in their respective definitions. The corresponding aspects between them are, however stronger than the differences, especially if one looks at the somatisation, the undifferentiated somatoform and the pain disorder, and recalls that their symptoms are all described as not fully explainable by a medical condition. In fact, it has been suggested that most of the multisymptom syndromes like somatoform disorders, fibromyalgia, CFS and exposure syndromes such as Gulf War illnesses, sick-building syndrome, illnesses found in women with silicon breast implants, multiple chemical sensitivity and others are related in terms of their stress-exposure histories, their psychological profiles, and some neurological alterations (Clauw D. Potential mechanisms in chemical intolerance and related conditions Ann NY Acad Sci 2001;933:235-253.). Controversy still exists as to whether syndromes consisting of subjective health complaints represent several or variations on one general condition (Ursin H. Eriksen HR. Sensitization, subjective health complaints and sustained arousal. NY Acad Sci 2001;933:119-129).

also of multisystem syndromes where the symptoms can't at present fully be ascribed to a specific medical condition. Low cortisol levels have been reported in various types of idiopathic pain and with gastrointestinal disorders for which no organic cause could be found. Typical examples of hypocortisolism in association with idiopathic pain include recurrent headaches, idiopathic chronic pelvic pain in women, recurrent abdominal pain in children and idiopathic pain in combination with functional gastrointestinal disorders. In most of these patients where low cortisol levels were found, there were also histories of poor coping abilities, multiple major stressful life events, and in women with chronic pelvic pain, high rates of physical and sexual abuse. Preliminary indications are that a degree of adrenal insufficiency and an above normal sensitivity to the negative feedback may underlie the hypofunction of the HPA-axis (173,179,180,183).

Chronic fatigue syndrome represents a multisystem condition for which no medical cause has been established beyond doubt, where idiopathic pain and fatigue form the core symptoms, where chronic stress or previous trauma or infection have been implicated in the onset, and where hypoactivity has been reported in subsets of patients. The CRH/HPA-axis disturbance would appear to entail enhanced negative feedback as well as suppression of central CRH-release (173). It would at present appear as if the hypocortisolism of somatisation-associated disorders differs from that of PTSD in that the somatoform disturbances may be characterised by a deficiency in central CRH drive, while in PTSD the central drive corresponds to that of other stress-related disorders, i.e., hyperactivity.

It is known that prolonged perceptions of uncontrollability of a stressful situation may give rise to hypoactivation of the CRH/HPA-axis – whether it be primarily central or peripheral in origin. Interesting research data indicate that such hypoactivity may, by rendering the individual hypoaroused and apathetic, also increase the vulnerable to drug abuse. Such individuals may then turn to cocaine, amphetamines or other drugs to stimulate their minds and to get them to a comfortable state of arousal (184).

The focus, throughout this chapter, was on the negative effects of the environment on the CRH/HPA-axis, i.e., the priming to hyperactivity or hypoactivity. It was shown how this can predispose to the development of mental disorders and disease. However, indications are that the environment and social interactions may also function as stress buffering mechanisms by correcting basal CRH/HPA activity and through blunting stress-induced activation of the axis (192). These results confirm what has already indirectly been implied by the success of psychotherapeutic interventions and social support systems, i.e., that social buffering can correct environmentally induced abnormalities in neurohormonal systems. This at least offers some hope for those in whom CRH/HPA-axis dysfunction occurs as a result of previous life experiences. It also leaves the field wide open for more relevant interdisciplinary research. In considering work in this area of research it is, however, important to remember that CRH/HPA activity plays a role in the determination of social preferences (192) and, by implication, could determine whether an event or even treatment would be perceived as a stressor, or as a stress buffering mechanism. From animal experimental work it would appear that some changes, such as the development of cortisol resistance, should perhaps be seen as adaptational rather than as pathological (192). Several aspects need further investigation in order to come to a clear understanding on the proposed transition from sickness behaviour to psychopathology. From the reverse point of view, i.e., the influence of emotions on the development of physical and to an extent mental disorders, there is an urgent need for studies to be performed in psychoneuroimmunological context. Some such studies have already been conducted (1,2) and it would appear that distress-related immune dysregulations may represent the core mechanisms underlying the health risks associated with negative emotions.

7.5 Summary

This chapter presented sickness behaviour as a model of the psychoneuroimmunological interaction. Sickness behaviour is often mistakenly seen as the negative side effect of physical illness – the result of debilitation and exhaustion. The depressive mood and other behavioural effects are generally considered emotional reactions to the illness and

To accept that sickness behaviour can develop into syndromes and disorders marked by multiple subjective health complaints one would expect to find indications of pro-inflammatory activity. There are reasons to suspect that an inflammatory process may be present in those subsets of individuals characterized by hypoactivity of the HPA-axis. The first and most obvious reason is that of a deficiency of cortisol – one of the most potent inhibitors of inflammation. In fact, as shown in Chapter 5, subnormal cortisol may even be immune-enhancing, rather than immune-stimulatory. In addition, it is known that IL-6 levels can be associated with chronic distress, feelings of uncontrollability and posttraumatic stress disorder (169). It is also known that cytokines can stimulate inflammatory pain and that IL-1 *per se* may lead to an increase in pain sensitivity in general (173,185), The picture with regard to the inflammatory cytokines in the disorders with HPA-axis hypoactivity are, however far from clear. Some authors reported increases in most of the pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha) (172,186,187) in chronic fatigue syndrome, but there are still many discrepancies in results. It seems necessary that researchers should subgroup their patients according to their HPA-axis activity and that psychiatric symptoms should be considered before investigating the immune status. Only then would it be possible to come to a better understanding on the immune status. However, even without proper empirical information on the pro-inflammatory status there are reasons to believe that sickness behaviour may render the individual vulnerable to the development of the somatoform and somatoform-related disturbances. The first reason is the similarity in symptoms. The second, more compelling, justification for the argument is that virtually all patients with clusters of subjective health complaints suffered either infectious complications – especially viral infections - or severe physical or emotional trauma (171). It has previously been shown that such events can initiate the development of sickness behaviour. It is also obvious that a hypoactivity of the HPA-axis can predispose to the development of inflammatory conditions and therefore to the inappropriate non-termination of sickness behaviour. Very interesting preliminary results that still need further investigation are that sickness behaviour can become a conditioned response (188,189,190,191). The implications speak for themselves.

debilitation. In this chapter it was shown that sickness behaviour should rather be seen as an adaptation to stress, i.e., a new adaptational homeostasis intended to aid in physical and psychological coping with the illness. The underlying mechanisms, as well as the adaptive value of the symptoms of sickness behaviour, were discussed. In line with Chapter 5 and Chapter 6 the central roles of the pro-inflammatory cytokines and the CRH/HPA-axis were illustrated and it was shown that cross-sensitisation can occur between the immunological (cytokines) and non-immunological stressors such as central neuroendocrine functions and cognitive phenomena like perceptions. Such cross-sensitisations can obviously influence the magnitude of the sickness behavioural symptoms, as well as the duration of the condition. Of additional importance is the fact that sickness behaviour can be initiated and maintained, not only by inflammatory or infectious conditions, but also by any form of tissue injury or psychological stress that alters the neuroimmunology balance towards a pro-inflammatory profile. It would, in fact, also appear as if sickness behaviour could be induced by conditioning.

Sickness behaviour, a condition afforded very little attention by the medical practitioner and seen largely as a reactive emotional state by psychologists, poses a potential threat to those rendered vulnerable to non-termination by their genetic makeup and early life presensitisation. Presensitisation, in the majority of cases, leads to hyperactivation of the major stress axes with a concomitant resistance to negative feedback to both the neurological systems and the pro-inflammatory cytokine activity. These characteristics are also present during sickness behaviour and constitutes characteristics of a number of mental disorders – including major depression of the melancholic type. The majority of the behavioural symptoms of sickness behaviour, which may range from mild constitutional disturbances to severe cognitive changes, result from the interaction between the pro-inflammatory cytokines and neurohormonal modulating systems such as the CRH/HPA-axis, the CNA/SAM-axis and the serotonergic system. Similar psychoneuroimmunological alterations marked by hyperactivity of the CRH/HPA-axis and the inflammatory response are seen in mental disorders such as major depression, the dysthymic disorder and, as classified by the DSM-IV, in depression due a general medical condition, as well as in other mental disturbances. In view of the similarities

between the neurohormonal, immunological and behavioural alterations of sickness behaviour and certain mental disorders, as well as the fact that non-terminations of sickness behaviour can occur due to early life predisposition and cross-sensitisation between non-cognitive and cognitive stimuli, it is postulated that sickness behaviour may, in certain circumstances, be the trigger for the development of mental disturbances. This hypothesis is particularly well supported by empirical evidence for mental disorders characterised by hyperactivity of the CRH/HPA-axis and pro-inflammatory activity. Despite the strong correspondence between the behavioural symptoms and possibly the presence of a cerebral inflammatory response in subsets of disorders associated with underactivity of the HPA-axis, research has not yet reached the point where an opinion can, with a fair amount of certainty, be expressed.

There can be no doubt that sickness behaviour represents a functional, adapted homeostasis intended to be of benefit to the individual. It is, however important to remember that sickness behaviour is in part a motivation state in which the afflicted individual is able to reorganize perceptions and behaviour within the existing internal and external limitations. In the knowledge that motivation states compete with each other for behavioural output, it is assumed that the hierachical organization of motivation states can be altered according to circumstances (193). In terms of sickness behaviour, any event perceived as more threatening than the illness may therefore transiently take precedence and the behaviour adapted to counter the new threat at the cost of the behavioural and physical adaptation for the illness. The expression of the behavioural aspects of sickness behaviour therefore becomes, within limits, a function of the individual's perceptions and needs. This, in line with stressor cross-sensitisation and the influence of cognitive functions, such as the perception of control, on the CRH/HPA-axis and immune status, thus also allows for a degree of modification of the biological symptoms of sickness behaviour by the psychological disposition - a good example of behaviour as biological response modifier. It is conceivable that, in certain individuals, sickness behaviour symptoms may consciously or subconsciously remain a preferred motivational state after recovery from the physical disorder. Such a condition, which

could possibly result from conditioning or the need to escape stressful situations, would contribute to the transition from sickness behaviour to psychopathology.

This chapter used sickness behaviour to illustrate the psychoneuroimmunological interaction in terms of the main stress axes. The central role of the CRH/HPA-axis and pro-inflammatory cytokines were described as major determinants of the sickness behavioural response and it was shown how psychological phenomena such as early life experiences and perception can act as biological response modifiers by altering the activities of the CRH/HPA-axis and the pro-inflammatory cytokines. The final sections of the chapter illustrated how sickness behaviour, which is intended as an adaptive homeostasis to facilitate coping and recovery, can, as a result of priming by negative life experiences, become the trigger for the expression of psychopathology. The next chapter will present conclusions on the thesis as a whole.

References

1. Kiecolt-Glaser JK, Mcguire L, Robles TF, Glaser R. Emotions, morbidity and mortality. New perspectives from psychoneuroimmunology. Ann Rev Psychol 2002;58:83-107.

2. Kiecolt-Glaser JK, Glaser R. Methodological issues in behavioral immunology research with humans. Brain Behav Immunol 1988;2:67-78.

3. Kiecolt-Glaser JK, Mcguire L, Robles TF, Glaser R. Zegans LS. Psychoneuroimmunology and psychosomatic medicine: Back to the future. Psychosom Med 2002;64:15-28.

4. Nature and nurture in psychiatry. A predisposition-stress model of mental disorders. Joel Paris. American Psychiatric Press, Inc, Washington DC, 1999.

5. Dantzer R, Bluthe RM, Castanon N, Chauvet N, Capuron L, Goodall G, Lelly KW, Konsman JP, Laye S, Parnet P, Pousset F. Cytokine effects of behaviour. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp703-725.

6. Rabin BS The nervous system-immune connection. In: BS Rabin. Stress immune function and health. Wiley-Liss, New York, 1999, pp145-148.

7. Charlton BG. The malaise theory of depression: major depressive disorder is sickness behavior and antidepressants are analgesics. Medical Hypotheses 2000;54(1):126-130.

8. Bolles RC. Species-specific defense reactions and avoidance learning. Psychol Rev 1970;77:32-48.

9. Aubert A, Kelly KW, Dantzer R. Differential effect of polysaccharide on food hoarding behaviour and food consumption in rats. Brain Behav Immun 1997;11:229-238.

10. Nicola NA. Guidebook to cytokines and their receptors. Oxford University Press, Oxford, 1994.

11. Dinarello CA. Biological basis for interleukin-1 in disease. Blood 1996;87:2095-2147.

12. Dantzer R, Bluthe RM, Castanon NC, Capuron L, Goodall G, Kelley KW, Konsman JP, Laye S, Parnet P, Pousset F. Cytokine effects on behavior. In R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp719-722.

13. Dunn AJ, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. In: R Dantzer, EE Wolmann, R Yirmiya (eds). Cytokines, stress and depression.. Advances in Experimental Medicine and Biology (vol461). Kluwer Academic/Plenum Publishers, New York, 1999, pp117-127.

14. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Trends in Neurosci 2002;25(3):154-160.

15. Breder CD, Saper CB. Expression of inducible cyclooxygenase mRNA in the mouse brain after systemic administration of bacterial lipopolysaccharide. Brain Res 1996;713:64-69.

16. Lacroix S, Rivest S. Effect of acute systemic inflammatory response and cytokines on the transcription of the genes encoding cyclooxygenase enzymes (COX-1 and COX-2) in the rat brain. J Neurochem 1998;70:452-466.

17. Wong ML, Rettori V, Al-Sheklee A, Boniorno PB, Canteros G, McCann SM, Gold PW, Licinio J. Inducible nitric oxide synthase gene expression in the brain during systemic inflammation. Nat Med 1996;2:581-584.

18. Dantzer R, Aubert A, Bluthe RM, Gheusi G, Cremona S, Laye S, Konsman JP, Parnet P, Kelley KW. Mechanisms of the behavioral effect of cytokines. In: Dantzer R, Wollman EE, Yirmiya R (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp83-105.

19. Kluger MJ, Kozak W, Mayfield KP. Fever and immunity. In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp687-702.

20. Wang WC, Goldman LM, Schleider DM, Appenheimer MM, Subjeck JR, Repsky EA, Evans SS. Fever-range hyperthermia enhances L-selectin-dependent adhesion of lymphocytes to vascular endothelium. J Immunol 1998;160:961-969.

21. Mackowiak PA. Fever: Basic mechanisms and management (2nd ed). Lippincott-Raven, Philadelphia, 1997.

22. Kozak W. Fever: A possible strategy for membrane homeostasis during infection. Pers Biol Med 1993;37:14-34.

23. Krueger JM, Fang J, Majde JA. Sleep in health and disease. . In: R Ader, DL Felten, N Cohen (eds). Psychoneuroimmunology (3rd ed, vol 1). Academic Press, San Diego, 2001, pp667-685.

24. Sluzewska A. Indicators of immune activation in depressed patients. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp59-73.

25. Leonard BE, Song C. Stress depression and the role of cytokines. In: NP Plotnikoff, RE Faith, AJ Murgo, RA Good (eds). Cytokines, stress and immunity. CRC Press, Boca Raton, Florida. 1999, pp251-266.

26. Hart B. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 1988;12:123-137.

27. Yirmiya R, Weidenfeld J, Pollak Y, Morag M, Morag A, Avitsur R, Barak O, Reichenberg A, Cohen E, Shavit Y, Ovadia H. Cytokines, 'depression due to a general medical condition', and antidepressant drugs. In: Dantzer R, Wollman EE, Yirmiya R. (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/Plenum Publishers, New York, 1999, pp283- 316.

28. Anisman H, Merali Z. Anhedonic and anxiogenic effects of cytokines. In: Dantzer R, Wollman EE, Yirmiya R (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/Plenum Publishers, New York, 1999, pp199-233.

29. Komaroff AL, Fagioli LR, Geiger AM, Doolittle DH, Lee J, Kornish J, Gleit MA, Guerriero RT. An examination of the working case definition of chronic fatigue syndrome. Am J Med 1996;100:56-64.

30. Koorts AM, Kruger MC, Viljoen M. Intracellular calcium and transmembrane calcium fluxes in chronic renal failure patients. Clin Physiol & Func Im 2002;22:285-294.

31. Jones THJ, Wadler S, Hupart KH. Endocrine-mediated mechanisms of fatigue during treatment with interferon-α. Sem Oncol 1998;25(suppl 1):54-63.

32. Kluger MJ. Fever: Role of pyrogens and cryogens. Phys Rev 1991;71:93-127.

33. Dantzer R, Bluthe RM, Kelley KW. Androgen-dependent vasopressinergic neurotransmission attenuates interleukin-1 induced sickness behavior. Brain Res 1991;557:115-120.

34. Zuckerman SH, Shellhaas J, Butler LD. Differential regulation of lipopolysaccharide-induced interleukin-1 and tumor necrosis factor synthesis: Effects of endogenous glucocorticoids and the role of the pituitary-adrenal axis. Eur J Immunol 1989;19:301-395.

35. Laye S, Goujon E, Combe C, VanHoy R, Kelley KW, Parnet P, Dantzer R. Effects of polysaccharides and glucocoticoids on the expression of interleukin-1β converting enzyme in the pituitary and brain of mice. J Neuroimmunol 1996;68:61-66.

36. Miller AH, Pariante CM, Pearce BD. Effects of cytokines on glucocorticoid receptor expression and function. Glucocoticoid resistance and relevance to depression. In: Dantzer R, Wollman EE, Yirmiya R (eds). Cytokines, stress and depression. Advances in experimental medicine and biology. (Vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp107-115.

37. Lakatos K, Toth I, Nemoda Z, Ney K, Sasvari-Szekely M, Gervai J. Dopamine D4 receptor (DRD4) gene polymorphism is associated with attachment disorganisation in infants. Mol Psych 2000;**5**:633-637.

38. Collins WA, Macoby EE, Steinberg I, Hetherington EM. Contemporary research on parenting: the case for nature and nurture. Am Psychol 2000;55(2):218-232.

39. Fonagy P. The human genome and the representational world: the role of early mother-infant interaction in creating an interpersonal interpretive mechanism. Bull Menninger Clin 2001;65(3):427-448.

40. Luecken LJ. Childhood attachment and loss experiences affect adult cardiovascular and cortisol function. Psychosom Med 1998;60:765-772.

41. Joseph R. Environmental influences on neural plasticity, the limbic system, emotional development and attachment: a review. Child Psych Hum Dev 1999;29(3):189-208.

42. Schore AN. Early organization of the nonlinear right brain and development of a predisposition to psychiatric disorders. Devel Psychopath;1997;9:595-631.

43. Schore AN. The experience-dependent maturation of a regulatory system in the orbital prefrontal cortex and the origin of developmental psychopathology. Devel Psychopathol 1996;8(1):59-87.

44. Taylor GJ, Parker JDA, Bagby RM. Emotional intelligence and the emotional brain: points of convergence and implications for psychoanalysis. J Am Acad Psychoanal 1999;27(3):339-354.

45. Henry JP. Psychological and physiological responses to stress: The right hemisphere and the hypothalamo-pituitary-adrenal axis, an inquiry into problems of human bonding. Acta Physiol Scand Suppl 1997;640:10-25.

46. Kotler T, Buzwell S, Romeo Y, Bowland J. Avoidant attachment as a risk factor for health. Br J Med Psychol 1994;67(3):237-45.

47. Joubert D, Reza Sadeghi M, Elliott M, Devins GM, Laperriere N, Rodin G. Physical sequelae and self-perceived attachment in adult survivors of childhood cancer. Psycho-Oncology 2001;10:284-292.

48. Gunnar MR. Quality of early care and buffering of neuroendocrine stress reactions: potential effects on the developing brain. Prev Med 1998;27:208-11.

49. Stuart S, Noyes R. Attachment and interpersonal communication in somatisation. Psychosomatics 1999;40:34-43.

50. Watson JS. Contingency perception and misperception in infancy: some potential implications for attachment. Bull Menninger Clin 2001;65(3):296-320.

51. Spangler G, Grossmann KE. Biobehavioral organization in securely and insecurely attached infants. Child Dev 1993;64(5):1439-50.

52. Bremner JD, Southwick SM, Johnson DR, Yehuda R, Charney DS. Childhood physical abuse in combat-related posttraumatic stress disorder. Am J Psychiatry 1993;150:235-9.

53. Dozier M, Chase Stovall KC, Albus KE. Attachment and Psychopathology in adulthood. In: Handbook of Attachment: Theory, Research and Clinical Applications. J. Cassidy, PR. Shaver (eds). The Guilford Press, New York. 1999. pp. 497-519.

54. Lynch M, Cichetti D. Trauma, mental representation, and the organization of memory or mother-referent material. Dev Psychopath 1998;10:739-759.

55. Phillips ML, Medford N, Senior C, Bullmore ET, Suckling J, Brammer MJ, Andrew C, Sierra M, Williams SCR, David AS. Depersonalisation disorder: thinking without feeling. Stress 2002;5(suppl):10.

56. Chorpita BF, Barlow DH. The development of anxiety: the role of control in the early environment. Psychol Bull 1998;124(1):3-21.

57. Corcos M, Atger F, Levy-Soussan P, et al. Bulimia nervosa and autoimmunity. Psychiatry Res 1999;87(1):77-82.

58. Suomi SJ. Attachment in Rhesus monkeys. In: Handbook of Attachment: Theory, Research and Clinical Applications. J. Cassidy, PR. Shaver (eds). The Guilford Press, New York. 1999. pp. 181-197.

59. Francis DD, Caldji FC, Champagne F, Plotsky PM, Meany MJ. The role of corticotropin-releasing factor-norepinephrine systems in mediating the effects of early experience on the development of behavioural and endocrine responses to stress. Soc Biol Psychiatry 1999;46:1153-1166.

60. Caldji C, Diorio J, Meaney J. Variations in maternal care regulate the development of stress reactivity. Biol Psychiatry 2000;48:1164-1174.

61. Levine S. Psychosocial factors in growth and development. In: Levi L (ed). Society, Stress and Disease. London, Oxford University Press, 1975, pp43-50.

62. Pacak K, Palkovits M, Kopin I, Goldstein DS. Stress-induced norepinephrine release in hypothalamic paraventricular nucleus and pituitary adrenocortical and sympathoadrenal activity: In vivo microdialysis studies. Front Neuroendocrinol 1995;16:89-150.

63. Francis DD, Meany MJ. Maternal care and the development of stress responses. Curr Op Neurobiol 1999;9(1):128-134.

64. Walker C-D, Toufexis DJ, Burlet A. Hypothalamic and limbic expression of CRH and vasopressin during lactation: implications for the control of ACTH secretion and stress hyporesponsiveness. Progress in Brain Res 2001;133:99-110.

65. Altemus M, Deuster PA, Galliven E, Carter CS, Gold PW. Suppression of hypothalamic-pituitary-adrenal axis responses to stress in lactating mothers. J Clin Endocrinol Metab 1995;80:2954-2959.

66. Champagne F, Meany MJ. Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsiveness. Prog Brain Res 2001;133:287-302.

67. Hennessy MB, Davis HN, McCrea AE, Harvey AT, Williams MT. Short- and long- term consequences of corticotropin-releasing factor in early development. Ann NY Acad Sci 1999;897:76-91.

68. Bakshi VP, Kalin NH. Corticotropin-releasing hormone and animal models of anxiety: gene-environmental interactions. Biol Psychiatry 2000;48:1175-1198.

69. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. CRF, depression and anxiety. J Endocrinol 1999;160:1-12.

70. Meany MJ, Diorio J, Francis D, Weaver S, Yau J, Chapman K. Postnatal handling increases the expression of cAMP-inducible transcription factors in the rat hippocampus: The effects of thyroid hormones and serotonin. J Neurosci 2000;20:3926-3395.

71. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. Biol Psychiatry 2001;49:1023-1039.

72. Cummings SL, Young WS, King JS. Early development of cerebellar afferent systems that contain corticotropin-releasing factor. J Comp Neurol 1994;350(4):534-549.

73. Calza L, Giardino L, Pozza M, Micera A, Aloe L. Time-course changes in nerve growth factor, corticotropin-releasing hormone and nitric oxide synthase isoforms and their possible role in the development of inflammatory response in

experimental allergic encephalomyelitis. Prog Nat Acad Sci USA 1997;94(7):3368-3373.

74. Hinde RA (ed). Primate social relationships: an integrated approach. Sinauer Associates, Suderland, 1983.

75. Lubach GR, Kittrell EM, Coe CL. Maternal influences on body temperature in the infant primate. Physiol Behav 1992;51:987-994.

76. Reite M, Seiler C, Short R. Loss of your mother is more than loss of a mother. Am J Psychiatry1978;135:370-371.

77. Andrews MW, Rosenblum LA. The development of affiliative and agonistic social patterns in differentially reared monkeys. Child Dev 1994;65:1398-1404.

78. Andrews MW, Rosenblum LA. Influences of environmental demand on maternal behavior and infant development Acta Paed Suppl 1994;397:57-63.

79. Harlow HF, Harlow MK. Effects of various mother-infant relationships on rhesus monkey behaviors. In: BM Foss (ed), Determinants of infant behavior (vol 4), Methuen, London,1969, pp15-36.

80. Sackett GP, Bowman RE, Meyer JS, Tripp RL, Grady SS. Adrenocortical and behavioral reactions by differentially raised rhesus monkeys. Phys Psychology 1973;1:209-212.

81. Gluck JP, Ozer H, Hensley LL, Beauchamp A, Mailman RB, Lewis MH. Early isolation in rhesus monkeys: Long-term effects on survival and cell-mediated immunity. Society of Neuroscience Abstracts 1989;15:197.

82. Worlein JM, Sackett GP. Social development in nursery-reared pigtailed macaques. Am J Primatol 1997;41:23-35.

83. Lubach GR, Coe CL, Ershler WB. Effects of early rearing environment on immune responses of infant rhesus monkeys. Brain Behav Immun 1995;9:31-46.

84. Shannon C, Champoux M, Suomi. SJ. Rearing condition and plasma cortisol in rhesus monkey infants. Am J Primatol 1998;46:311-321.

85. Mineka S, Suomi SJ. Social separation in monkeys. Psychol Bull 1978;85:1376-1400.

86. Bowlby J. Attachment and loss II. Separation: anxiety and anger. Basic Books, New York, 1973.

87. Levine S, Weiner SG. Psychoendocrine aspects of mother-infant relationships in non-human primates. Psychoneuroendocrinology 1988;13:143-154.

88. Kraemer GW, Ebert MH, Schmidt DE, McKinney WT. Strangers in a strange land: A psychobiological study of infant monkeys before and after separation from real or inanimate mothers. Child Dev 1991;62:548-566.

89. Laudenschlager ML, Boccia ML, Berger CL, Gennaro-Ruggles MM, McFerran B, Reite ML. Total cortisol, free cortisol, and growth hormone associated with brief social separation in young macaques. Dev Psychobiol 1995;28:.199-212.

90. Laudenschlager ML, Reite M, Harbeck RJ. Suppressed immune response in infant monkeys associated with maternal separation. Behav Neural Biol 1982;36:40-48.

91. Coe Cl, Rosenberg LT, Levine S. Prolonged effect of psychological disturbance on macrophage chemiluminescence in the squirrel monkey. Brain Behav Immun 1988;2:151-160.

92. Coe CL, Rosenberg LT, Levine S. Effect of maternal separation on the complement system and antibody responses in infant primates Int J Neurosci 1988;40:289-302.

93. Coe CL, Erickson CM. Stress decreases lymphocyte cytolytic activity in the young monkey even after blockade of steroid and opiate hormone receptors. Dev Psychobiol 1997;30:1-10.

94. Laudenschlager ML, Rasmussen KLR, Berman CM, Suomi SJ, Berger CL. Specific antibody levels in free-ranging rhesus monkeys: Relationship to plasma hormones, cardiac parameters and early behavior. Dev Psychobiol 1993;26:407-420.

95. Boccia ML, Laudenschlager ML, Reite ML Intrinsic and extrinsic factors affect infant responses to maternal separation. Psychiatry 1994;57:43-49.

96. Kagan J Snidman N, Julia-Sellers J, Johnson MO. Temperament and allergic symptoms. Psychosom Med 1991;53:332-340.

97. Cacioppo JT. Social neuroscience: autonomic neuroendocrine and immune responses to stress. Psychophysiol 1994;31:113-128.

98. Caine N, Reite M. The effect of peer contact upon physiological response to maternal separation. Am J Primatol 1981;1:271-276.

99. Laudenschlager ML, Held PE, Boccia ML, Reite ML, Cohen JJ. Behavioral and immunological consequences of brief mother-infant separation: A species comparison. Dev Psychobiol 1990;23:247-264.

100. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Social ties and susceptibility to the common cold. J Am Med Assoc 1997;277:1940-1944.

101. Suomi SJ, Harlow HF, Domek CJ. Effect of repetitive infant-infant separation on young monkeys. J Abn Psychol 1970;76:161-172.

102. Scanlan JM, Coe CL, Latts A, Suomi SJ. Effects of age, rearing and separation stress on immunoglobulin levels in rhesus monkeys. Am J Primatol. 1987;13:11-22.

103. Laudenschlager ML, Berger CL, Boccia ML, Reite ML. Natural cytotoxicity towards K562 cells by macaque lymphocytes from infancy through puberty. Effects of early social challenge. Brain Behav Immun 1966;10:275-287.

104. Capitanio JP, Lerche NW. Psychosocial factors and disease progression in simian AIDS: A preliminary report. AIDS 1991;5:1103-1106.

105. Gordon DP, Gust DA, Wilson ME, Ahmed-Ansari A, Brodie AR, McClure HM. Social separation and reunion affects immune system in juvenile rhesus monkeys. Phys Behav 1992;51:467-472.

106. Gust DA, Gordon DP, Wilson ME, Brodie AR, Ahmed-Ansari A, McClure HM. Removal from natal social group to peer housing effects cortisol levels and absolute number of T-cell subsets in juvenile rhesus monkeys. Brain Behav Immun 1992;6:189-199.

107. Boccia ML, Scanlan JL, Laudenschlager ML, Berger Cl, Hijazi AS, Reite ML Juvenile friends, behavior, and immune responses to separation in bonnet macaque infants. Physiol Behav 1997;61:191-198.

108. Gust DA, Gordon TP, Brodie AR, McClure HM. Effects of a preferred companion in modulating stress in adult female rhesus monkeys. Physiol and Behav 1994; 55:681-684.

109. Capitanio JP, Lerche NW. Social separation, housing relocation, and survival in simian AIDS: A retrospective analysis. Psychosom Med 1998;60:235-244.

110. Gust DA, Gordon TP, Wilson ME, Brodie AR, Ahmed-Ansari A, McClure HM. Formation of a new social group of unfamiliar female rhesus monkeys affects the immune and adrenocortical systems. 1991;5:296-307.

111. Boccia Ml, Reite ML, Laudenschlager ML. On the physiology of grooming in pigtail macaques. Physiol Behav 1989;45:667-670.

112. Gust DA, Gordon TP, Hambridge MK, Response to removal from and return to social group in adult male rhesus monkeys. Physiol and Behav 1993;53:599-602.

113. Cohen S, Kaplan JR, Cunnick JE, Manuck SB, Rabin BS. Chronic social stress, affiliation and cellular immune response in non-human primates. Psychol Sci 1992;3:301-304.

114. Cunnick JE, Cohen S, Rabin BS, Carpenter AB, Manuck SB, Kaplan JR. Alterations in specific antibody production due to rank and social instability. Brain Behav Immun 1991;5:357-369.

115. Boccia ML, Laudenschlager ML, Broussand CL, Hijazi AS. Immune responses following competitive water tests in two species of macaques.Brain Behav Immun 1992;6:201-213.

116. Alberts SC, Sapolsky RM, Altman J. Behavioral, endocrine and immunological correlates of immigration by an aggressive male into a natural primate group. Hormones and Behav 1992;26:167-178.

117. The Fourth World Congress on Stress, Edinburgh, UK, September 12-15, 2002.

118. Shekhar A, Sajdyk TJ, Rainnie DG, Gehlert. CRH-induced plasticity in the amygdala: a putative link between stress and human illness. Stress 2002;5(suppl):24.

119. Ingram CD, Fairchild G, Johnson DA, Troakes C, Lowry C, Lightman, SL, Gartside SE. CRH and glucocorticoid actions on raphe serotonergic neurons. Stress 2002;5(suppl):24.

120. Matthews SG, Owen D, Banjanin S, Andrews MH. Glucocorticoids, endocrine development and life after birth. Stress 2002;5(suppl):26.

121. Plotsky PM, Walker CD, Garlow SJ. Persistent changes in central nervous system gene expression in response to repeated neonatal separation. Stress 2002;5(suppl):27.

122. Grunau RE. Early repetitive stress in preterm infants: effects on behaviour and development. Stress 2002;5(suppl):27.

123. Heim C. Neurobiological correlates of early adverse experience in women. Stress 2002;5(suppl):28.

124. Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear, anxiety and allostatic load. Psychoneuroendocrinology 1998;23(3):219-243.

125. Armario A. A single exposure to a severe stressor causes long-term desensitization of the physiological response to the homotypic stressor. Stress 2002;5(suppl):16.

126. Sanchez MM, Anand KJS. Long-term consequences of early painful experiences. Stress 2002;5(suppl):17.

127. Morilak DA. A modulatory role of norepinephrine in behavioural stress responsiveness and susceptibility to stress-related pathology. Stress 2002;5(suppl):25.

128. Phillips DIW. Fetal growth, the HPA axis and the metabolic syndrome. Stress 2002;5(suppl):28.

129. Walker CD, Proulx K, Richard D, Salzman CX, Gallo-Payet N. Leptin enhances glucocorticoid feedback sensitivity while limiting stimulated adrenal corticosterone release in rat pups. Stress 2002;5(suppl):29.

130. Brunton PJ, Russel JA. Endogenous opioids are involved in reduced neuroendocrine responses to immune challenges. Stress 2002;5(suppl):52.

131. Douglas AJ, Bosch O, Toschi N, Neumann ID. Stress hyporesponsiveness during parturition in the rat: antagonising brain oxytocin does not reveal an inhibitory influence. Stress 2002;5(suppl):54.

132. Levay PF, Viljoen M, Meij HS. Oksitosien: 'n Kort oorsig. Die Suid Afrikaanse Tydskrif vir Natuurwetenskap en Tegnologie 1993;12(3)61-66.

133. Ma S, Shipton MJ, Russel JA. Roles of neurosteroids in the attenuated hypothalamo-adrenal-pituitary (HPA) axis stress response in pregnant rats. Stress 2002;5(suppl):58.

134. De Kloet, Oitzl MS, Meijer OC, Karssen AM, Datson NA, Feldker DEM, Vreugdenhil E. Glucocorticoid signalling and responsive genes: implications for behavioural adaptations. Stress 2002;5(suppl):30.

135. Hsu SY, Hsueh AJ. Human stresscopin and stresscopin-related peptide are selective ligands for the type 2 corticotropin-releasing hormone receptor. Nature Medicine 2001;7(5):605-611.

136. Welberg LA, Seckl, JR, Holmes MC. Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotropin-releasing hormone: possible implications for behaviour. Neuroscience 2001;104(1):71-79.

137. Weinstock M. Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? Neurosci Biobehav Rev 1997;21(1):1-10.

138. Sheline YI, Wang PW, Gado MK, Csernansky JG, Vannier WW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci 1996; 93:3908-3913.

139. Miller AH, Pariante CM. Effects of cytokines on glucocorticoid receptor expression and function. In: R Dantzer, EE Wollman, R Yirmiya (eds). Cytokines, stress and depression. Advances in Experimental Medicine and Biology, Vol 461. Kluwer Academic/Plenum Publishers, New York, 1999, pp107-127.

140. Ruiz M, Lind U, Gafvels M, Eggertsen G, Nilsson L. Characteristics of two novel mutations in the glucocorticoid receptor gene in patients with primary cortisol resistance. Clin Endocrinol 2001;55(3):363-371.

141. Smith RS. The macrophage theory of depression. Medical Hypothesis 1991; 35:298- 305.

142. Maes M. The interleukin hypothesis of major depression. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:11-35.

143. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, DC, 1994, pp317-389.

144. Bouwer C, Claassen J, Dinan TG, Nemeroff CB. Prednisone augmentation in treatment-resistant depression with fatigue and hypocortisolaemia: a case series. Depression and Anxiety 2000;12(1):44-50.

145. Yirmiya R, Weidenfeld J, Pollack Y, Morag M, Morag Y, Avitsur R, Barak O, Reichenberg A, Cohen E, Shavit Y, Ovadia H. Cytokines, depression due to a general medical condition and antidepressant drugs. In: Robert Dantzer, Emmanuelle E Wollman, Yirmiya R. Cytokines stress and depression. Advances in Experimental Medicine and Biology (vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp283-307.

146. Lindhorst ACE, Reul JMHM. Inflammation and brain function under basal conditions and during long-term elevation of brain corticotropin-releasing hormone levels. In: Robert Dantzer, Emmanuelle E Wollman, Yirmiya R. Cytokines stress and depression. Advances in Experimental Medicine and Biology (vol 461). Kluwer Academic/ Plenum Publishers, New York, 1999, pp129-152.

147. Maes M, Bosmans E, Meltzer HY, Sharpe S, Suy E. Interleukin-1β: a putative mediator of HPA axis hyperactivity in major depression? Am J Psychiatry 1993;150:1189-1193.

148. Chrousos GP. Stressors, stress and neuroendocrine integration of the adaptive response. NY Acad Sci 1998;851:311-355.

149. Maes M, Meltzer HYM. The serotonin hypothesis of major depression. In: F Bloom, D Kupher (eds) Psychopharmacology: the fourth generation of progress. Raven Press. New York, 1995, pp933-944.

150. Buckingham JC, Loxley HD, Christian HC, Philip JG. Activation of the HPA axis by immune insults: roles and interactions of cytokines, eicosanoids, and glucocorticoids. Pharmacol Biochem Behav 1996;54:285-288.

151. Maes M. Major depression and activation of the inflammatory response system. In: R Dantzer, EE Wollman, R Yirmiya. Cytokines, Stress and Depression, Advances of Experimental Medicine and Biology, Vol 461, Kluwer Academic/Plenum Publishers, New York, 1999, pp25-46.

152. Nicoloff JT, LoPresti JS. Non-thyroidal illness. In: LE Braverman, RD Utiger (eds). The thyroid: A functional and clinical text. JB Lippencott Company, New York, 1991, pp357-367.

153. Spath-Schwalbe E, Hansen K, Schmidt F, Schrezenmeier H, Marshall L, Burger K, Fehm HL, Born J. Acute effects of human recombinant interleukin-6 on endocrine and central nervous sleep functions in healthy men. J Clin Endocrinol and Metab 1998;83:1573-1579.

154. Haag M. Poly-unsaturated fatty acids: cellular role and clinical applications. The Medical Journal 2001;43:13-17.

155. Maes M, Christophe A, Bosmans E, Lin A, Neels H. In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychological stress. Biol Psychiatry 2000;47(10):910-920.

156. Merrill JE. Tumor necrosis factor alpha, interleukin 1 and related cytokines in related brain development: normal and pathological. Dev Neurosci 1992;14:1-10.

157. Charlton BG. The malaise theory of depression: major depressive disorder is sickness behavior and antidepressants are analgesics. Medical Hypothesis 2000;54(1):126-130.

158. Lee R, Spencer PSJ. Antidepressants and pain: a review of the pharmacological data supporting the use of certain tricyclics in chronic pain. J Internat Med Res 1997;5(suppl 1):146-156.

159. Portnoy RK, Kanner RM. Pain management: Theory and Practise. FA Davis, Philadelphia, 1996, pp226-229.

160. McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB. Depression inpatients with cancer: diagnosis, biology and treatment. Arch Gen Psychiatry 1995;52:89-99.

161. Muller M, Ackenheil M Psychoneuroimmunology and the cytokine action in the CNS: implication for psychiatric disorders. Prog Neuropsychopharmacol Biol 1998;22;1-33.

162. Kasckow JW, Baker D, Geratioti TD. Corticotropin-releasing hormone in depression and post-traumatic stress disorder. Peptides. 2001;22:845-851.

163. Chochinov HM, Wilson KG, Enns M, Lander S. Prevalence of depression in the terminally ill. Effects of diagnostic criteria and symptom threshold judgements. Am J Psychiatry 1994;4:537-540.

164. Katon W, Sullivan MD. Depression and chronic medical illness. J Clin Psychiatry 1990;51:3-11.

165. Isometsa ET, Aro HM, Henrikkson MM, Heikkinen ME, Lonnqvist JK. Suicide and major depression in different treatment settings. J Clin Psychiatry1994;55:523-537.

166. Smith AP, Tyrrell DAJ, Al-Nakib W, Coyle KB, Donovan CB, Higgins PG, Willman JS. The effects of experimentally induced respiratory virus infections and illness. Psychology and Health 1988;5:205-212.

167. Hickie I, Lloyd A. Are cytokines associated with neuropsychiatric syndromes in humans? Int J Immunopharmacol 1995;17:677-683.

168. Schiffer RB, Babigian HM. Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis. An epidemiological study. Arch Neurol 1984;41:1067-1069.

169. Reif W, Pilger F, Ihle D, Bosmans E, Maes M. Immunological differences between patients with major depression and somatization syndrome. Psychiatry Res 2001;105:165-174.

170. Maes M, Song C, Lin A, Jongh RD, Van Gastel A, Kenis G, Bosmans E, De Meester I, Benoy I, Neels H, Demedts P, Janca A, Scharpe S, Smith RS. The effects of psychological stress on humans: Increased production of proinflammatory cytokines and a Th-1 like response in stress-induced anxiety. Cytokine 1998;10:313-318.

171. Clauw DJ. Potential mechanisms in chemical intolerance and related conditions. Ann NY Acad Sci 2001;933:235-253.

172. Visser JTJ, De Kloet ER, Nagelkerken L. Altered glucocorticoid regulation of the immune response in chronic fatigue syndrome. Ann NY Acad Sci.2000;917:868-875.

173. Ehlert U, Heinrichs JGM. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. Biol Psychol 2001;57:141-152.

174. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, DC, 1994, p424.

175. Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geratioti TD. Serial corticotropin-releasing hormone levels and adrenal cortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry 1999;156:585-588.

176. Stein MB, Yehuda R, Koverola C, Hanna C. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatizes by childhood abuse. Biol Psychiatry 97;42:680-686.

177. Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, Najarian LM, Fairbanks LA. Basal cortisol, dexamethasone suppression of cortisol and MHPG in adolescents after the 1988 earthquake in Armenia. Am J Psychiatry 1996;153:929-934.

178. Wang S, Wilson JP, Mason JW. Stages of decompensation in combat-related posttraumatic stress disorder: a new conceptual model. Integr Physiol Behav 1996;31:237-253.

179. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 2000;25:1-35.

180. Heim C, Newport DJ, Wilcox M, Bonsall R, Miller AH, Nemeroff CB. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. J Am Med Assoc 2000;284:592-597.

181. Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 1996;40:1091-1099.

182. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, DC, 1994, pp445-469.

183. Heim C, Ehlert U, Hanker JP, Hellhamer DH. Abuse related posttraumatic stress disorder and alterations of the hypothalamic-pituitary-adrenal axis in women with chronic pelvic pain. Psychosom Med 1998;60:309-318.

184. Majewska MD HPA axis and stimulant dependence: and enigmatic relationship. Psychoneuroendocrinology 2002;27:5-12.).

185. Schaefer M, Stein C. Control of pain in peripheral tissue by cytokines and neuropeptides. In: NP Plotnikoff, Faith RE, Murgo AJ, Good RA. Cytokines, stress and immunity. CRC Press, Boca Raton, FL,1999, pp261-270.

186. Strauss SE, Chronic fatigue syndrome: point and counterpoint. J Infect Dis 1994;170:1-6.

187. Komaroff AL. Chronic fatigue syndrome: an update. Ann Rev Med 1998;49:1-13.

188. Bull DF, Brown R, King MG. Modulation of body temperature through taste aversion conditioning. Physiol Behav 1991;49:1229-1233

189. Exton MS, Bull DF, King MG. Behavioural conditioning of lipopolysaccharide-induced anorexia. Physiol Behav 1995;57:401-405.

190. Janz LL, Green-Johnson J, Murray L. Pavlovian conditioning of LPS-responses: effects on corticosterone, splenic NE, and IL-2 production. Physiol Behav 1996;59:1103-1109.

191. Bull DF, Exton MS, Husband AJ. Acute phase immune response: lipopolysaccharide-induced fever and sleep alteration are not simultaneously conditionable in the rat during the active phase (light) phase. Physiol Behav 1994;56:143-149.

192. DeVries AC. Interaction among social environment, the hypothalamic-pituitary-adrenal axis, and behaviour. Horm Behav 2002;41:405-413.

193. Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Ann NY Acad Sci 2001;933:222-234.

CHAPTER 8

CONCLUSIONS

Psychoneuroimmunology is a developing interdisciplinary field that deals with the interactions between the psychological aspects, the interconnected neurological functions, and the related immunological processes. Unlike previous approaches to the mind-body paradox it introduces the immune system into the equation.

This thesis shows the central role of corticotropin-releasing hormone (CRH) and the pro-inflammatory cytokines in the psychoneuroimmunological approach to the mind-body interaction. It is concluded that psychoneuroimmunology in terms of the two major stress axes can largely be equated with psychoneuroimmunology in terms of CRH and that immunologically derived cytokines constitute the major interface between peripheral somatic events and the behavioural functions. It is clear that disturbances in the cytokine balance, a phenomenon previously associated mainly with physical disease, are of equal importance with regard to the development of abnormal behaviour and psychiatric symptomatology. In contrast to some previously published suggestions, particular patterns of cytokine activity should not summarily be considered as correlates of specific behavioural outcomes as the effects are largely determined by baseline neurohormonal activity and reactivity which, in turn, depends on predisposition by early psychosocial experiences and genetic disposition. Resilience and vulnerability factors at the time of the stressor onslaught may either decrease or increase the probability for the expression of the specific psychopathology as determined by the predisposition and precipitated by the stressor, in this case the immune dysregulation.

In addition, the thesis introduces the concept of sickness behaviour as precipitating factor for the development of mental disturbances in individuals so predisposed by previous life experience. It may be asked in what way this concept differs from the predisposition-stress model of mental disorders, i.e., whether the introduction of the concept of sickness behaviour as precipitating factor for the development of mental disorders makes any new contribution to our understanding of psychology or

psychiatry. The answer is contained in two facts. The first is that the coordinated set of behavioural changes that constitutes sickness behaviour represents a new homeostasis or state of adaptation intended to aid in coping with whatever stressor threatened the primary homeostasis. It is therefore the coping mechanism and not the initiating stressor that gives rise to the psychopathology. The second difference lies in the fact that sickness behaviour as syndrome of adaptation already consists of emotional, cognitive and physical changes that correspond to psychopathological states and that it is merely the prerequisite of non-termination of the adaptation process that determines the transition of sickness behaviour, as process of coping and adaptation, to a state of psychopathology with related symptoms. It is also important to note that it is the inappropriate continuation of a normal adaptive homeostasis which, in this thesis, is proposed as the cause of the mental disturbance and, in contrast to Darwinian approaches to the etiology of mental disorders, not a maladaptive variant of the adaptive response.

It can with confidence be said that psychoneuroimmunology provides the link between a number of previously unexplained associations between behaviour and disease. Many of these associations were made long before the existence of either psychiatry or immunology as independent disciplines, some dating as far back as Aristotle, Galen and Hippocrates. More recently, several hypotheses were described on viral or specific immunological activity as part of the etiology of mental disturbances such as depression, schizophrenia, chronic fatigue syndrome, multiple sclerosis and certain neurodegenerative disorders. Support for most of them waned as the presence of the suggested viral infection or immune alteration could very often not consistently be confirmed. The concept of cytokine involvement in the vulnerability to, and in the development of, mental disorders gives credence to these hypotheses if one remembers that it is most probably the non-specific cerebral inflammatory response and not any specific virus or other micro-organism, or even localized cerebral or other trauma, that constitutes the final pathway of most of these disturbances.

In addition, psychoneuroimmunology helps us to understand the cross-sensitisation between cognitive and non-cognitive stressors. It is, for instance, of great importance to realize that stress-induced activation of the CRH/HPA-axis, as well as the

production of pro-inflammatory cytokines, can be initiated through stressors as diverse as infections or negative emotions and perceptions, and that the effects of such stressors can be cumulative. It is more than likely that these biological aspects of the stress response can, at least partially, be reversed by positive emotions. This last aspect is a vastly under-researched area of psychoneuroimmunology and holds a wide range of research possibilities for mental health workers. Of equal importance is the fact that the relative non-specificity with regard to the initiating stressor is mirrored in the type of pathology which could develop from the same precipitating stressor which may vary from mild personality changes to overt psychopathology or even physical disease – depending on the nature of the predisposition. This apparent non-specificity with regard to the type of pathology that can develop carries the unfortunate implication that immune disturbances, as is the case for other biological markers, cannot in isolation be used as markers for specific mental disturbances. What it can do is to contribute to identification of the nature of the psychosocial factors that gave rise to the biological predisposition. It is tempting, and very feasible, to speculate that assessment of the pro-inflammatory/anti-inflammatory cytokine balance may find practical application as prognostic indicator in mental disorders. In this context reversal of immune disturbances may provide a convenient prognostic index of the success of psychotherapy and other interventions. This potential needs to be properly researched, as the possibility has, to the best of my knowledge, not yet been investigated

In view of the fact that the inflammatory reaction underlies a host of mental and physical disorders and that it may be a key factor in general physical deterioration, frailty and disability, coupled to the fact that negative emotional states and stressful experiences, high allostatic loads and cross-sensitisation between stressors can stimulate the production of pro-inflammatory cytokines, it is essential that the immune status be considered when investigating the psychophysiology of stress or health. There are, in fact, indications that stress-induced immune disturbances may be the fundamental mechanisms underlying the health risks imposed by negative emotions.

There can be no doubt that psychoneuroimmunology brings us one step closer to the understanding of the total interconnectiveness of body and mind. It is essential to

stress that the psychoneuroimmunological approach does not in any way detract from the value of existing biological or psychological approaches to health or disturbances thereof. In fact, the validity of opposing theories is in certain cases rather strengthened by the link psychoneuroimmunology provides between more reductionistic biological and environmental approaches. The pervasiveness of the psychoneuroimmunological interaction does indeed necessitate a paradigm shift in our approach to illness, be it primarily physical or mental in presentation.

Although psychoneuroimmunology can be seen as extension of the stress paradigm and helps to explain the mechanism underlying the interactions proposed by models such as the biopsychosocial and other approaches, much of the scientific evidence was initially derived from studies in neuroimmunomodulation. The majority of scientific studies are therefore from the biomedical field. While some relevant work has been published by psychiatrist abroad, there is a dire need in South Africa for the input of mental health workers, as well as for solid interdisciplinary cooperation between the behavioural and biomedical sciences, in the execution of psychoneuroimmunological studies with local relevance.