

# Stress and Strain

## Their Definition, Psychobiology and Relationship to Psychosomatic Medicine

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### Introduction

More than 40 definitions of stress can be found in the literature<sup>1</sup>. This confusion could occur because stress is usually put on a par with the total process of adaptation, without this process even being analyzed. Upon analysis, three terms appear to be important, i.e. load, strain and stress (Fig. 1).

In biology, the process of adaptation particularly applies to the homeostasis of the organism. Load is any factor, chemical, physical, psychic or social, which is capable of disturbing the homeostasis. Strain is then any change in homeostasis brought about by the load in the organism. And stress is any reaction in the organism provoked by the strain which serves to restore the original equilibrium. In these definitions it is essential that all load should first be converted into changes in the organism (strain), before it acquires any significance for the organism. Moreover, in this model stress is by definition wholesome to the organism. All pathogenic changes in the organism under load, i.e. changes that may bring about a specific disorder, syndrome or disease, are by definition reckoned with the strain.<sup>2 3 4 5 6</sup>

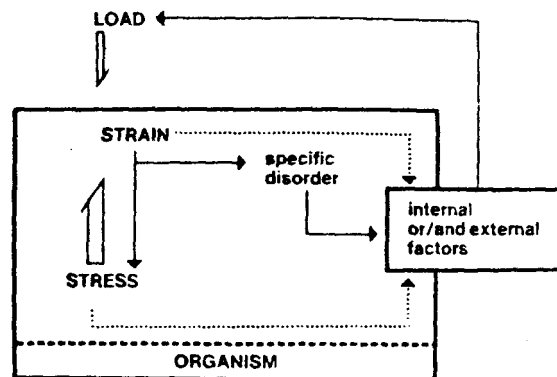
When we say that "stress has given someone a heart attack", we hence mean that loading factors have caused such a strain in the organism, that stress has not compensated for the strain and that strain has provoked a heart attack as a specific disorder. Strain is accompanied with anxiety (free-floating anxiety) as psychic

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Because strain possibly has a pathogenic significance, it is important that strain be recognized and measured. For this purpose anxiety can be taken as a measure or, as research has suggested, the excretion of xanthurenic acid in urine after intake of L-tryptophan.<sup>2 6</sup>

**FIG.1**  
**THE LOAD-STRAIN-STRESS MODEL**

Selye<sup>7</sup> has described the general adaptation syndrome (GAS) as an adaptation process that



occurs in three phases: i.e. those of alarm, adaptation and exhaustion. In this connection he defines stress as "the non-specific response of the body to any demand". This is, in fact, too wide a definition<sup>2 8</sup> (Selye, personal communication, 1982). Indeed, he had started his investigation with the study of what he called "the syndrome of being sick". It had struck him that sick people, irrespective of their specific disorder, have many characteristics in common: tired appearance, lack of energy, weakness, lack

of appetite etc., in brief: their being sick. This is typically strain. In a recent leading article in *TIME* (June 6, 1983, pp. 42-52) on stress, "the rate of wear and tear in the body" was quoted as a definition by Selye. This, too, is typically strain. Only the real "response" to the strain can be considered stress. From this model it appears how specific disorders, such as myocardial infarction, gastric ulcer, depression, etc. can be kept separated from the process of adaptation. Genetic factors determine the susceptibility to the specific disorder, which is formed in the development, and therefore they are of another order than strictly aetiological factors, such as strain. The changes of strain and stress take place in the organism in a homeostasis which is genetically codetermined<sup>7</sup>. The genetics of strain and stress, however, are in no way connected with those of the specific disorder.

It is now important that in the exhaustion phase of the GAS the reserves (energy) of stress have been used up and that in this phase the risk of provoking specific disorders (by strain) is maximal<sup>10</sup>. Moreover, during the emotions of the alarm phase the transient strain can become too strong and, e.g. via the sympathetic nerve system, provoke a heart attack.

### **Eustress and Distress — Strain and Stress**

Selye has defined stress as a "nonspecific response", i.e. a number of characteristic changes in the organism under load, e.g. the classical triad of adrenal cortex hyperplasia, thymus atrophy and gastric ulcer<sup>7</sup>. He completely disregards the nature of the stimulus<sup>11</sup>. Selye discerns the response in favorable and unfavorable effects for the organism. He calls the favorable effects "eustress" and the unfavorable ones "distress". As indicated in the previous chapter, Selye's definition of stress falls into two components, i.e. strain and stress. As long as stress can keep the strain in balance, the condition is favorable. In the alarm phase there may be a temporary disturbance, but in the adaptation phase the organism has restored its balance of adaptation. But if the load lasts too long or if it is too heavy

the organism uses up its reserve energy in maintaining homeostasis. When this has occurred, the exhaustion phase is reached. Then strain is predominant. The risk of pathological events is hence present in the alarm phase and the adaptation phase, and is maximal in the exhaustion phase. When strain is predominant, one can speak of being unwell. The balance between strain and stress is inherent in life. Life is inconceivable without load. As long as the balance of strain and stress is maintained, one's adaptation process is exercised and this is favorable. This is a condition of being well.

### **Load Can Have A Therapeutic Value**

According to Selye, energy consumption is inherent in stress, if for no other reason than for keeping the control mechanisms of homeostasis operational. Life is full of load. When this is encountered, strain is experienced and stress is activated. Exercising the interplay between strain and stress is favorable because it trains the organism in an efficient energy consumption as a function of adaptation. The better the stress is exercised, the better it can compensate for the strain, and the lower the risks of strain assuming pathogenic proportions.

With regard to this exercising, it should be noted that heavy load on the organism at too young an age has an unfavorable effect. Histopathologic techniques in experimental animals have demonstrated that load at a young age leads to a detectable inhibition of brain growth<sup>12</sup>.

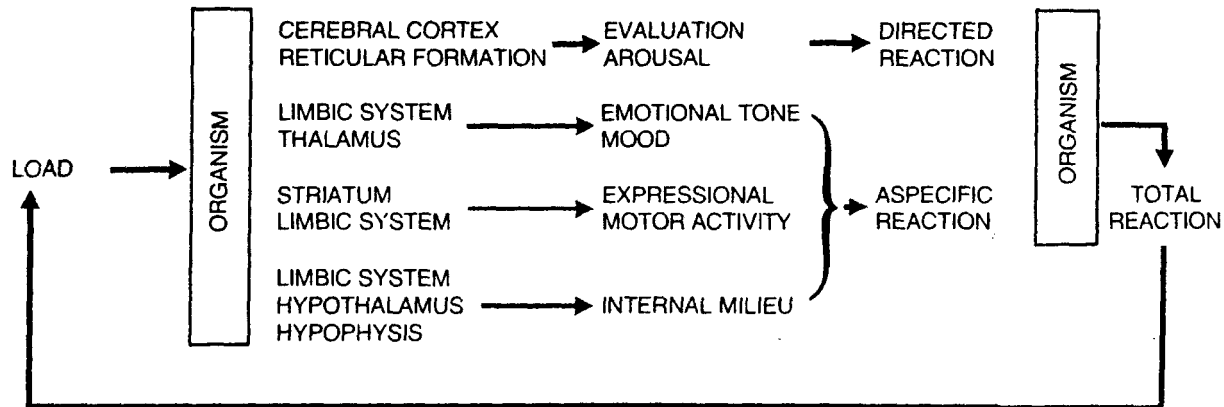
The excretion of adrenal cortex hormones under the influence of ACTH is increased during strain. It has also been observed in experimental animals that adrenal cortex hormones may inhibit the growth and development of the cerebrum<sup>15</sup>. Even in adults one must realize that strain parameters such as ACTH<sup>14</sup> and Cortisol<sup>15</sup> may affect behavior and mood, besides having an endocrinological effect. Hence when one proceeds from strain and stress as original endocrino-logically defined reactions, it appears that

several parameters, particularly cerebral ones, must be taken into account. The brain controls behavior as well as the secretion of ACTH and is, in turn, influenced

by ACTH and Cortisol, e.g. in the hippocampus<sup>16</sup>, an important region with regard to mood and feeling well<sup>17</sup>.

**FIG. 2**

**THE CEREBRAL ORGANIZATION OF THE REACTION TO LOAD**



The directed component of the reaction tries to solve the problem that has given rise to the load. The aspecific component of the reaction is the strain in which the compensatory stress is incorporated.

**Physical Load May Have A Favorable Effect on the Sequels of Mental Load**

When a person is confronted with a certain loading factor, a number of processes occur in the brain (Fig. 2). The stimulus of load is observed. This results, on the one hand, in a directed response to the stimulus, while, on the other hand, aspecific processes are activated as strain-stress<sup>17</sup>.

A) For the directed component the cerebral cortex is essential. The reticular formation of the mid-brain and thalamus (centre median, lamina mediana interna and externa, reticular nucleus) activates the cerebral cortex thereby. Via the dor-sosmedial nucleus of the thalamus this part of the reaction also acquires an emotional tone.

B) The cerebral substrates for the aspecific component of the reaction may be discerned in:

(1) The reticular formation which controls arousal.

(2) Furthermore, the limbic system is involved via aspecific afferents which reach the rhinencephalon. This limbic system has in septum, hippocampus, mid-brain parts and hypothalamus structures which are of vital importance for eliciting emotions, e.g. in the alarm phase of adaptation or mood changes (an emotion is an intentionless,

excited condition of the organism, characterized by autonomous-physical and visceral-motor disorders; mood is a feeling, with intention)<sup>2</sup>.

(3) The striatum is involved as third structure. Clinical<sup>18</sup> as well as pharmacological<sup>19</sup> studies have demonstrated that the striatum is of particular importance for the motor activity of expression, the organization and planning of motor activity.

(4) Eventually the hypothalamus and hypophysis, as specific export stations of the limbic system, organize the neuroendocrine and autonomous-vegetative changes, that belong to the aspecific part of the reaction.

The total reaction upon load may thus be represented as consisting of two main components, the directed and the aspecific part. The aspecific part, i.e. the strain, is in its components particularly affected by the 4 major anatomical structures.

Selye has indicated that as the motor component of strain is inhibited, the intensity of the neuroendocrine component increases<sup>7</sup>. So within the organization of the aspecific part of the reaction, mutual shifts in activity between the organizing parts are possible. It can thus be imagined well that increase of motor activity, in

sports and games, can result in a decrease of total strain and certainly of, e.g. the autonomous-vegetative and neuroendocrine component of strain. Autonomous-vegetative and neuroendocrine strain can provoke specific disorders such as gastric ulcer and myocardial infarction. Arousal, too, will decrease

when practicing sports. This is greatly welcomed, since the creation of a well directed response requires a certain degree of arousal, not too low (sleep), nor too high (anxiety, excitement)<sup>11</sup>. Thus, when practicing sports, one's strain and stress organization is trained and a directed response is facilitated.

## THE LIMBIC SYSTEM

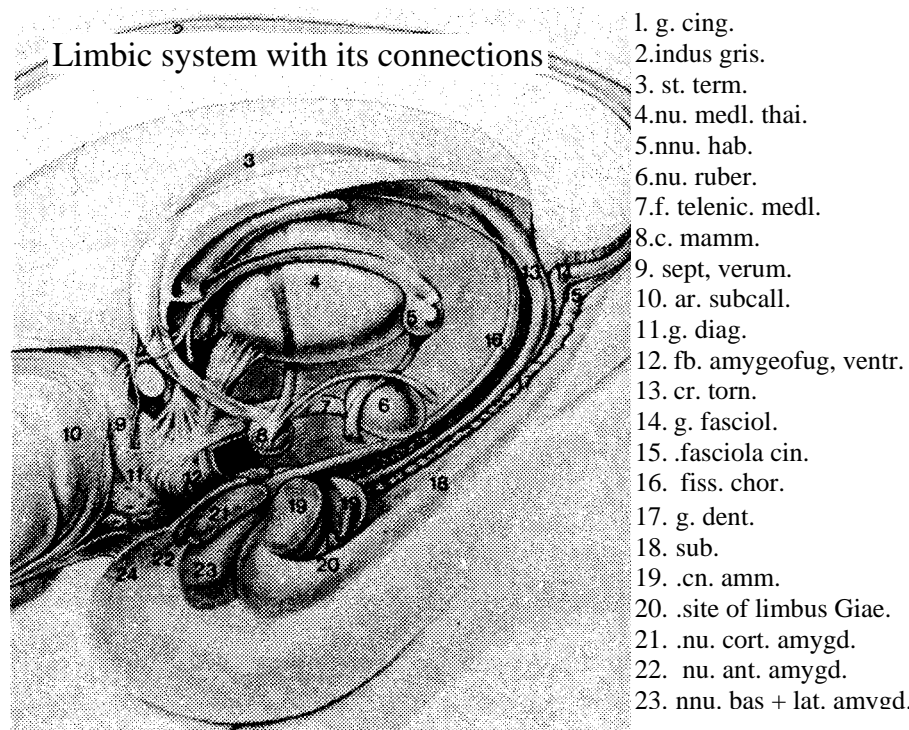
### A. Circuits

The limbic system consists of the older brain parts (Fig. 3), the palaeopallium and archipallium, which combined are called allopallium<sup>17 20 21 22 23</sup>, in contrast to the neopallium, the cerebral cortex. It is situated as a ring (limbus) between the diencephalon and telencephalon. Broca was, in 1878, the first person to use the term 'limbic' in the description of the 'grand lobe limbique', by which he combined the area parolfactoria, gyrus ginguli, isthmus gyri cinguli, gyrus hippocampi, now called

### SOME MAJOR STRUCTURES OF THE LIMBIC SYSTEM

parahippocampi. In 1937, Papez described the so-called circuit of Papez in an article which has become famous, i.e. "A Proposed Mechanism of Emotion". He rescued the field from oblivion. Maclean has also performed a lot of investigation and introduced the term 'limbic system'. He also indicated by the term "schizophysiology" that the limbic system can act independently from the cortex although it usually acts in combination with it. The limbic system comprises the smell brain and is, phylogenetically speaking, a very old area.

FIG. 3



(Reproduced from Nieuwenhuys et al.<sup>25</sup> with permission of the authors and Springer Verlag, Heidelberg.

There are three main circuits in the system.

- (1) A circuit runs from the amygdaloid nucleus, via the induseum griseum and gyrus cinguli to the septal nuclei. The diagonal band of Broca forms the following link between amygdala and septum.
- (2) From the hippocampus the fornix leaves to the septum, area preoptica, hypothalamus, corpora mamillaria. From the corpora mamillaria the bundle of Vicq d'Azyr leaves to the anterior nucleus thalami and from the corpora mamillaria the pedunculus tegmenti runs to the mid-brain. From the anterior nucleus thalami strong projections to the frontal cortex and to the anterior part of the gyrus cinguli are found. From there, the hippocampus can be reached again via the cingulum. This is the circuit of Papez.
- (3) Further, the stria terminalis runs from the amygdala to the septum. The septum can communicate with the amygdala via the diagonal band of Broca. Besides that, there is a strong projection from the hypothalamus and the amygdala to the dorsomedial nucleus thalami.

The paleocortex consists of hippocampus, subiculum, gyrus dentatus, gyrus fasciolaris and indusum griseum.

## B. Function

The paleocortex is essential for the sense of smell and the organization of mood, instinctive behavior with regard to self-preservation and preservation of the species, with the accompanying somatomotor (e.g. respiration), autonomous-physical and visceral activities. This organization occurs in association with the septum, hypothalamus and mid-brain. The archicortex, which composes the remainder of the limbic system, plays a predominant mediating role in instinctive emotions, feelings and emotional and affective expression patterns. The orbito-insulo-temporal area and the rostral

pyriform cortex are of essential importance in mood changes. From the gyrus cinguli and the orbito-insulo-temporal area, sniffing and emotional respiratory motions are effected, and from the rostral part of the pyriform cortex and the amygdaloid nucleus complex licking, chewing and swallowing movements. The amygdaloid nucleus constitutes a sensory expression of visceral and somatosensory stimuli, and furthermore organizes autonomous-physical and endocrine functions. The archicortex forms the so-called Es-brain, a spontaneous analyzer, an instinctive evaluating cortex part. The hippocampus serves for the integration of (1) sensory stimuli, (2) unconscious evaluation of stimuli as to usefulness/damage, desire-non-desire for the organism, (3) the memory of senses and (4) the organization of emotions, feelings and their expression, and also consciousness.

## C. Input and Output

The sensory information that reaches the organism is transmitted to the specific thalamus nuclei, to the reticular formation, as discussed above, and to the archipallium<sup>24 25</sup>. Hippocampus and amygdala can thus work out the integration and emotional evaluation of these stimuli. When they have made the evaluation at instinctive usefulness-damage level, the behavior programme is organized in association with septum, hypothalamus, mid-brain and striatum (psychomotor activity).

Via the anterior and dorsomedial nuclei thalami there are extensive connections with the cerebral cortex, so that the emotional aspect can be both intrinsically connected with the homeostatic changes, controlled by the limbic system, and connected to the directed cortical reaction to the stimulus.

## D. Mood

Anxiety is, as already mentioned, the psychic aspect of strain. Anxiety may change into depressiveness upon persisting

strain<sup>26</sup>. Anxiety and depressiveness are mood disorders. With regard to mood the limbic system is important, as already mentioned above. Even more important is the thalamus, which as evaluation organ of the fundamentally physical condition is essential in mood. This may be due to the fact that it both receives the specific sensory information, as the arousal stimuli via the thalamic reticular formation, and the information from the limbic system (anterior and dorsomedial nuclei thalami) and from the cerebral cortex.

### **E. Strain and Stress**

In the described structures and their connections of the limbic system in association with the thalamus, the neural organization of strain is again found, with its arousal, autonomous-physical, visceral, somatomotor and mood aspects.

In the organization that has now been discussed, areas can be indicated which are essential for stress because it has been demonstrated that they inhibit certain areas of the described strain organization. This applies, for instance, to the serotonergic raphe nuclei which inhibit the noradrenergic nuclei<sup>27</sup>, to the septum which inhibits the hippocampus<sup>28 29 30</sup>, to the caudal reticular formation which inhibits the rostral part, the ascending reticular activating system (ARAS)<sup>31 32</sup> and to the anterior hypothalamus (parasympathetically) which inhibits the posterior hypothalamus area (sympatheticus)<sup>33</sup>.

### **The Function of the Basal Ganglia**

Obviously Parkinson's disease is our major source of knowledge about the function of the basal ganglia in man<sup>18</sup>, particularly of the substantia nigra and the striatum. The patient with Parkinson's disease shows personality disorders, his mood is often depressive, furthermore there are disturbances in the motor activity, in the senses, particularly of smell, and vegetative regulations, e.g. sweat and sebum secretion. From neuro-anatomical<sup>25</sup> and neuro-surgical<sup>34</sup> investigations it appears that the striatum has a direct effect on the function of the thalamus, which could play a part

in depressive mood. Further analysis demonstrates that the striatum, as the junction of pyramidal and extrapyramidal system, is important in stature regulation, in the preparation of movements and triggering thereof and in the strategy planning of psychic functions and behavior<sup>19</sup>. Besides being rigid, akinetic and tremorous, the Parkinson patient is also careful, cautious, non-creative, tense, excited, uneasy, phobic, even psychasthenic. In other words, he shows a loss of suppleness of motor activity as well as behavior. The basal ganglia mediate this suppleness, particularly in the expression of motor activity. Furthermore, the basal ganglia are important for the feedback regulation of neuroendocrine and autonomous-vegetative nature, even though this function is more global than for instance in the hypothalamus<sup>18 19</sup>.

### **The Benzodiazepine and Opiate Receptors**

Subcellular membrane particles have been found in the brain to which benzodiazepines specifically bind, i.e. the so-called benzodiazepine receptors. These receptors appear to belong to a larger receptor complex, namely that of the GABA receptor.

GABA is gamma-aminobutyric acid, our major inhibiting neurotransmitter. Antiepileptics, alcohol and convulsants such as strychnine or pentylenetetrazol also act on this GABA receptor complex<sup>35 36</sup>. When one discusses the benzodiazepine receptor and its role in the suppression of anxiety<sup>37</sup> a few restrictions should be kept in mind. Diverse agents, such as alcohol, do not act directly on the benzodiazepine receptor but still have an anxiolytic effect. The connection with the benzodiazepine action is possibly found in the GABA receptor complex on which diverse substances with anxiolytic (and anticonvulsive) effect act. Upon activation of the benzodiazepine receptor the GABA receptor is facilitated and a physiological inhibitory effect is exerted on neurotransmission. The septo-hippocampal system is

greatly important for the development of anxiety<sup>29 30</sup>. It may then be assumed that anxiolytics inhibit the neurophysiologic activity in such an area, probably via the GABA receptor complex, and thus diminish anxiety and strain. Moreover, this action is not specific for anxiolysis, since benzodiazepines possess, besides anxiolytic properties, also muscle-relaxant, anticonvulsive and hypnogenic characteristics. In analogy with the situation of the benzodiazepine receptor, binding material for opiates has also been found in the brain, the so-called opiate receptors. The latter have been known for a longer time than the benzodiazepine receptors. Natural agonists of these receptors have been detected, the peptides, endorphines and enkephalins. As we know these agents certainly play a part in analgesia<sup>38</sup> and hence in desire-non-desire experience. Further it is known that the limbic system is full of opiate receptors<sup>26</sup>. However, a specific role in strain or anxiety has not yet been found. Investigations in man up to now mainly concerned the possible antipsychotic activity of the endorphines<sup>39</sup> besides their analgesic effect<sup>38</sup>. No connection between the opiate and benzodiazepine or GABA receptor has been observed.

### Strain In The Psychosomatic Daily Practice

For the practitioner it is important that he pays attention to symptoms of strain -because strain may be pathogenic - in the alarm phase, possibly in the adaptation phase and certainly in the exhaustion phase of the GAS. This can be discerned from anxiety and possibly quantified by measuring the excretion of xanthurenic acid<sup>2 6</sup>. When strain lingers on, anxiety may become chronic, or (associated with pain) change into depressiveness (not necessarily the 'major depressive disorder')<sup>26</sup>. In case of strain, it is possible that the physician does not come across anxiety as a complaint, but the patient may, for instance, complain of sleep disorders. It has been demonstrated that in case of anxiety the deep stages of sleep are lacking. Due to this lack the patient does not get enough physical rest<sup>40</sup> and becomes tired. Strain provokes specific disorders and therefore the field of psychosomatic medicine should be

particularly studied with regard to strain<sup>10</sup>.

### Conclusion

In this article, recent insights into strain and

stress have been represented. The biological fundamentals of the adaptation process occupy an important place with regard to this<sup>41</sup>. On the basis of this, several therapeutic possibilities can be conceived, particularly of chemotherapy of strain<sup>5 42 43</sup>. The main point of any therapy should be to reduce strain and promote stress.

### Synopsis

The adaptation process is discerned in load, strain and stress. Each load is converted in the body into strain, for which the organism compensates under the form of stress. When one becomes ill due to load, strain is the pathogenic link in the organism. In that case strain provokes a certain syndrome or disorder. Each load brings about a reaction in the individual, consisting of a specific part directed towards the stimulus, and an aspecific part. The specific part is particularly effected via the cerebral cortex. The aspecific part (strain) is particularly organized in association with the reticular formation, limbic system, striatum and hypothalamus. This part consists of emotional-affective, psychomotor, neuroendocrine and autonomous-vegetative reactions. In the reticular formation, limbic system and hypothalamus, components are indicated which because of their inhibitory effect on other parts, may serve as substrate of stress. Via the anterior and dorsomedial nuclei thalami, the aspecific part of the reaction can be formed to a total reaction

with the specific part. The possible role of the benzodiazepine and opiate receptors is discussed. It is important for psychosomatic medicine that this psychobiologic model shows how stress and strain are organized. The model gives more insight into the somatic treatment of strain. **References**

1. DIJKHUIZEN, N. VAN: From stressors to strains. Swets en Zeitlinger, Lisse 1980.
2. HOES, M.J.A.J.M.: L-tryptophaan in depressie en strain. Academisch Proefschrift, Nijmegen 1981.
3. HOES, M.J.A.J.M.: Depression, anxiety, load, strain, stress and the metabolism of L-tryptophan. *Stress*, 3 (3): 19-24, 1982.
4. HOES, M.J.A.J.M.: Monoamines in Psychiatry, *Acta psychiat Belg.* 82; 287-309, 1982.
5. HOES, M.J.A.J.M.: Pharmacotherapie du syndrome d'hyperventilation. *Ann. Med. - Psychol.* 141 (8), 859-874, 1983.
6. HOES, M.J.A.J.M.: The excretion of xanthurenic acid in 24 hours urine after oral intake of 5 grammes L-tryptophan: a measure of strain in the organism. In: Selye H. (editor), *Selye's guide to stress research*, vol. 3. Van Nostrand Reinhold New York, 86-99, 1983.
7. SELYE, H.: *Stress in Health and Disease*. Butterworths, London, nervous mechanisms 932-1018, 1976.
8. REES, L.W.: Stress, distress and disease. *Br. J. Psychiat.* 128: 3-18, 1976.
9. FARBER, S.L.: Genetic diversity and differing reactions to stress. In: *Handbook of stress. Theoretical and clinical aspects*. Goldberger L., Breznitz S. (editors) Free Press MacMillan New York, 123-134, 1983.
10. SELYE, H.: Psychosomatic disease. *Stress* 3 (3): 4, 1982.
11. COX, T.: *Stress*. MacMillan, London, 1978.
12. STURROCK, R.R., SMART J.L. and TRICKLEBANK M.D.A. Quantitative neurohistological study of the long-term effects in the rat brain of stimulation in infancy. *J. Anat* 136 (1): 129-144, 1983.
13. DEVENPORT, L.D. and DEVENPORT, J.A.: The effects of adrenal hormones on brain and body size. *Physiol, psychol.* 10 (4): 399-404, 1982.
14. FEKETE, M., BOHUS B. and DE WIED, D.: Comparative effects of ACTH-related peptides on acquisition of shuttle-box avoidance behavior of hypophysectomized rats. *Neuroendocrinology* 36(2): 112-118, 1983.
15. CARPENTER, W.T. and GRUEN P.H.: Cortisol's effects on human mental functioning. *J. Clin. Psychopharmacol.* 2(2): 91-102, 1982.
16. ANGELUCCI, L., PATACCHIOLI, F.R., SCACCIANOCA, S., MARTUCCI E., and CAPASSO, M.: Hippocampal glucocorticoid binding: serotonergic regulation and drug effects; relevance to behavioral-endocrine activities and depression. *Ann. 1st. Super. Sanita*, 18(1): 35-40, 1982.
17. PRICK, J.J.G.: De biologische grondslag van hysterische gedragswijzen. In: *Nederlands handboek der psychiatrie*, vol. 2 de neurosen. Prick J.J.G., Waals H.G. van der, (editors) Van Loghum Slaterus, Arnhem. Hoofdstuk V. 345-418, 1963.
18. KORTEN, J.J.: *De paralysis agitans-ziekte*. Stafleu, Leiden, 1970.
19. COOLS, A.R. and BERCKEN, J.H.L. VAN DEN: Cerebral organization of behavior and the neostriatal function In: Cools A.R., Lohman A.H.M., Bercken J.H.L. van den (editors). *The psychobiology of the striatum*. North Holland Amsterdam 119-141, 1977.
20. SAACSON, R.L.: *The limbic system*. Plenum Press New-York, 1983.
21. LIVINGSTON, K.E., and HORNYKIEWICZ, O.: *Limbic mechanisms*. Plenum Press, New-York, 1978.
22. PENFIELD, W., and JASPER, H.: *Epilepsy and the functional anatomy of the human brain*. Little Brown, Boston, the limbic lobe 177-179, 1954.
23. TRUEX, R.C., and CARPENTER M.B.: *Strong and Elwyn Human Neuroanatomy* 5th edit. Williams and Wilkins Co., Baltimore chapter 20, Rhinencephalon, olfactory pathways, and limbic system, 443-460, 1964.
24. KEVETTER, G.A., and WILLIS, W.D.: Collaterals of the spinothalamic cells in the rat. *J. comp. Neurol*, 215 : 453-464, 1983.
25. NIEUWENHUYIS, R., VOOGD. J., and HUIJZER CHR. VAN: The human central nervous system. Springer Verlag, Heidelberg, the so-called extrapyramidal system 166-177, and the olfactory and limbic systems 181-212, 1979.
26. HOES, M.J.A.J.M.: *Psychobiologie van de pijn*. TGO/JDR 5, 773-784, 1980.
27. ECCLES, J.C.: *The human psyche*. Springer Verlag, Heidelberg, 1980.
28. GROSSMAN, S.P.: An experimental dissection of the septal syndrome. In: *ibidem als Weiskrantz*, 227-260.
29. GRAY, J.A.: Anxiety as a paradigm case of emotion. In: Warburton D.M., Summerfield A (editors). Churchill Livingstone, London. *Br. med. Bull.* 37 (2): 193-199, 1981.
30. WEISKRANTZ, L.: Functions of the septo-hippocampal system. CIBA Foundation symposium. no. 58 (new series) Excerpta Medica, Amsterdam, 1978.
31. MAGOUN, H.W.: *The waking brain*, second edit. Thomas, Springfield, 1963.
32. MORUZZI, G.: The sleep-waking cycle. *Erg. z. Physiol.*, 64, 1-165, 1972.



33. AKERT, K.: Biological order and brain organization. Selected works of W.R. Hess Springer Verlag, Heidelberg, 1981.
34. WALDER, H.A.D. Toepassing van de cryotherapie in de neurochirurgie. In: Walder H.A.D., Bekke J.P.H., Brinkman W.F.B. et al. Toepassing van de cryochirurgie in de geneeskunde Stafleu, Leiden 9-60, 1978.
35. BRAESTRUP, C, NEILSEN, M. Anxiety Lancet II, 1030-1034, 1982.
36. DELIGNE, P., MAK, D., AND RICHARD, P.: Neuro-mediation inhibitrice gaba-ergique et mode d'action des benzodiazepines. Conv. Med. 1(3): 215-224, 1982.
37. SMYTHIES, J.R.: Biochemical aspects of neurotic behavior. In: Pragg H.M. van, Lader H.M., Rafaelsen O.J., Sachar E.J. (editors) Handbook of biological psychiatry, Vol.IV: Chemistry. Marcel Dekker, Basel 343-355, 1981.
38. GEBHART, G.F.: Opiate and opioid peptide effects on brain stem neurons: relevance to nociception and antinociceptive mechanisms Pain 12: 93-140, 1980.
39. VERHOEVEN, W.M.A.: Endogenous opioids and gamma-type endorphins in schizophrenia. Academisch Proefschrift, Utrecht, 1983.
40. ROSA, R.R., BONNET, M.H., KRAMER, M.: The relationship of sleep and anxiety in anxious subjects. Biol. Psychol. 16: 119-126, 1983.
41. HOES, M.J.A.J.M.: Psychosomatische geneeskunde: op weg naar de psychobiologie van gezond en ziek zijn. TGO/JDR 5: 737-742, 1980.
42. WALKER, J.I.: Chemotherapy of traumatic Was stress. Mil. Med. 147 (12): 1029-1033, 1982. 43. HOES, M.J.A.J.M. Farmacotherapie van het hyperventilatiesyndroom TGO/JDR 8, 1881-1888, 1983,1,