bio|vis' DIAGNOSTIK

Chronic Stress and its Consequences

A red-hot topic
in the modern practice

Dear colleagues,

We live in stressed times. The demands increase, multi-tasking is daily routine and even our free time is stress. Everyone, who does not have stress is almost looked upon as “out”. But stress is more than a temporary fashion; it is a serious medical pro- blem. If it persists for a longer period of time it may lead to complete exhaustion of a human being and may rush him headlong into a deep crisis – physically as well as emotionally – and may make him unable to work.

According to the Report of Accident Prevention of the Federal Government about 50% of all employees live under permanent time and performance pressure, 30% even work at the limit of their performance capacity. Even worse are the implications: only one third of all employees do not suffer from work related somatic, psychosomatic and emotional complaints.

Because of the permanent release of stress hormones and neu- rotransmitters in case of chronic stress the body heads slowly but surely in the direction of exhaustion – burn-out or chronic fatigue syndrome.

In this small brochure you

- **can find out how such events manifest in your patients**
- **can find out how you can diagnose it easily and quickly**
- **are provided with first therapy recommendations**

If you have further questions, please call us we will gladly pro- vide more information and advice.

With the best wishes for your health

Ihr

Burkhard Schütz

What Is Stress And Who Has Stress?

Stress is a serious medical problem to be considered. If there is a long-term stress condition – it might become chronic – this will lead to absolute exhaustion of a person and may cause physical and psychological illness and inability to work.

Stress may be understood as disproportion between demands on the person con- cerned and his individual compensation capacity like positive experiences, self- affirmation, relaxing and the like. If this gets out of balance the person concerned gets under "pressure" – he feels "stressed". There may be different factors causing this imbalance: existential fear, problems in the relationship or the family, juveniles may have problems in school or adults difficulties at work. In general a high mea- sure of heteronomy may produce stress just like physical disorders, for example persistent pain or traumata.

If the acquired stress protection mechanisms of the person concerned do not suf- fice in such stress situations, acute stress is produced. If this disproportion persists for a longer period of time, chronic stress will develop. And this will sooner or later lead to disease symptoms – **emotional and physical exhaustion, burn-out syndrome** or **CFS** (chronic fatigue syndrome).

Persons with multiple responsibilities are particularly at risk, often women with family and job, but also men in "their prime age", who do not recognize the limits of their performance capacity. This also applies for people, who feel completely at someone's mercy or whose daily work is redundant and gives them little power of decision and not last the "perfectionist", to whom 100% are never good enough.

The Stress Response Of The Body

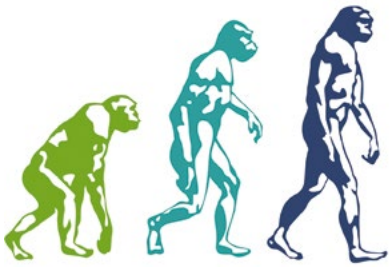
Stress activates the so-called neuro-endocrine function axis of the body. It consists of

- the **ultra-fast, adrenergic stress response**, which leads to catecholamine re- lease within seconds after the stress impulse and
- the **delayed endocrine response**, which releases the corticotrophin releasing hormone (CRH), formed by noradrenalin produced from the Locus caeruleus in the hypothalamus. This again releases the adreno-corticotrope hormone (ACTH) from the anterior pituitary and promotes the secretion of cortisol from the adrenal gland within a few minutes.

The Most Important Factor: Cortisol

Cortisol is our most **important stress hormone**. It is produced from cholesterol and leads to reactions of the organism, which allow the **body to cope** with the stress situation. For this purpose it causes an increase of **blood pressure, blood sugar** and **the triglyceride level in blood**. Thereby it provides **lots of energy** quickly. The person concerned could rescue himself out from the stress situation – **by fighting or escaping** – as it was necessary during our "animal" past. Also the **pain suppres- sion and mental activation**, which produced cortisol, were right and important in this context.

Today this does not make much sense any more, as it is only rarely possible to solve modern stress situations by running away or physical defence. For this reason the- se cortisol effects stress the body as it cannot use the sudden high energy supply for physical action, but has to assimilate it otherwise – for example by **releasing large amounts of insulin**. In addition there are other effects of the stress hormone. Cortisol for example reduces the blood circulation of skin and intestines as the blood is needed more urgently in the brain, the heart and the muscles to be ready to fight or escape.



If there is not only a single stress situation but permanent stress, cortisol is released constantly and the described **physical reactions** take place all the time. The body compensates the high cortisol levels to a certain extent, which means its reaction becomes less, but nevertheless, permanently, high blood pressure strains the organs, just like increased blood sugar. Due to the reduced intestinal blood circulation digestive disorders are pre-programmed. In addition cortisol blocks the **cellular immune response**: The natural killer cells as well as the T- helper cells are suppressed. This makes stressed people susceptible to **infections** and promotes **tumour progression**.

If the stress condition exists for a very long period of time the stress hormone production in the adrenal cortex will exhaust: the person concerned is tired, has no motivation, many physical complaints occur and every task whatsoever seems to be an extreme effort

THE DIAGNOSTICS: CORTISOL IN SALIVA

WITH SIMPLE SALIVA TESTS YOU CAN FIND OUT THE STRESS LOAD OF YOUR PATIENTS. FOR THIS PURPOSE A **CORTISOL DIURNAL** PROFILE SHOULD BE MADE (ONE SALIVA SAMPLE EACH IN THE MORNING, AT MID-DAY AND IN THE EVENING).

THE NORMAL DEVELOPMENT OF A CORTISOL DIURNAL **PROFILE** SHOWS A MAXIMUM LEVEL IN THE MORNING – ABOUT ONE TO TWO HOURS AFTER WAKING UP. THEN THE VALUES DECREASE CONTINUOUSLY IN THE COURSE OF THE DAY TO REACH A SMALL PEAK AGAIN IN THE EARLY AFTERNOON AND FINALLY REACH THE MINIMUM LEVEL IN THE EVENING. IN CASE OF AN ACUTE STRESS SITUATION THE CORTISOL LEVELS INCREASE TEMPORARI-LY. THIS MAY INFLUENCE ONE, TWO OR ALL THREE MEASURING VALUES.

DURING THE FIRST PHASE OF LONG-TERM **CHRONIC STRESS** ONE GEN-ERALLY FINDS INCREASED CORTISOL LEVELS FOLLOWED BY DECREASING SALIVA HOR- MONE CONCENTRATIONS. IN THE BEGINNING THERE ARE OFTEN ONLY DEC- REASED VALUES IN THE MORNING, LATER ALSO THE OTHER CORTISOL VALUES FALL BELOW AVERAGE. REDUCED CORTI-SOL LEVELS ARE CHARACTERISTIC FOR PATIENTS SUFFERING FROM **BURN-OUT** OR **CHRONIC FATIGUE SYNDROME**.

The Antagonists of Cortisol

Important antagonists of cortisol are dehydroepiandrosterone (DHEA) and mela- tonin.

DHEA – just like cortisol – is regulated by ACTH and is produced in the adrenal cortex. It has positive effects on blood lipid values by decreasing LDL choles-terol and increasing the HDL cholesterol. Furthermore it improves the immune condition by stimulating the cellular immune response, has an anti-inflamma-tory effect and increases insulin sensitivity.

In case of **chronic stress** the DHEA production – just like the cortisol produc-tion – is first increases, only to decrease below nominal range in the further course. Ne- vertheless also the DHEA production is **age-related**. Humans between the age of 20 and 30 have the highest synthesis rate. In the further course of life the ability of the adrenal cortex to produce DHEA continuous-

ly decreases. For this purpose there might be **increased stress sensitivity** in old age as the cortisol antagonist is missing but cortisol production is undiminished.

Melatonin is the other cortisol antagonist, which is released in higher quantities by the pineal gland in case of stress. Melatonin stimulates the immune system, has tumour inhibiting effects and counteracts cortisol also by decreasing the blood pressure. Aside from that it is very important for a normal **circadian rhythm**. Melatonin is produced only by transformation of **serotonin** – an important neurotransmitter – which plays a central role in diagnostics and therapy of chronic stress, burn-out and some other diseases – see below. If there is a serotonin deficiency the body automatically also lacks melatonin.

THE DIAGNOSTICS: MELATONIN IN URINE

FOR THE DETERMINATION OF MELATONIN THE **FIRST VOID URINE** IS REQUIRED. IN THIS SAMPLE THE MELATONIN REQUIRED FOR DETERMINING THE NIGHTLY TOTAL PRODUCTION OF THE CORTISOL ANTAGONIST IS MEASURED. ESPECIALLY IF A PATIENT COMPLAINS ABOUT SLEEP DISORDERS TESTING MELATONIN LEVEL MAY CLARIFY THE CAUSES.

Other Stress Relevant Messengers: Catecholamines, GABA and Glutamate

The **catecholamines** adrenaline, noradrenalin and dopamine are released within seconds during the ultra-fast stress response.

Adrenalin produced in the adrenal medulla causes an increase of pulse rate, cardiac output (per minute), blood pressure and mental activity. At the same time it inhibits the cellular immune activity.

Also **noradrenalin** released from Locus caeruleus in midbrain and adrenal cortex increases the blood pressure, promotes performance readiness, concentration, motivation and motor functions. It also inhibits the cellular immune response.

And at last **dopamine** is released from the adrenal medulla and is an important excitatory neurotransmitter. Similar to noradrenalin it has a positive effect on motor functions, concentration, performance readiness, motivation and cognitive activity. All catecholamines evolve from the precursor tyrosine – a non-essential proteinogenic amino acid - which is produced from the essential amino acid phenylalanine. If there is a phenylalanine deficiency, tyrosine also has to be substituted.

Catecholamines – other than cortisol – are quickly decomposed by the body– their half-life is only a few minutes.

GABA, ɣ-amino-butyric-acid is the most important inhibiting neurotransmitter in the central nervous system. It counteracts the excitatory catecholamines and also lessens the endocrine stress response. GABA stabilizes the blood pressure, controls the appetite, has an anxiolytic effect and promotes sleep. It is synthesized from glutamine acid – a non-essential amino acid, which functions as excitatory neurotransmitter in the central nervous system and can also be regarded as antagonist of GABA. Glutamine acid supports motor functions, learning and memory.

THE DIAGNOSTICS: CATECHOLAMINES, GABA AND GLUTAMATE IN URINE

FOR THE DETERMINATION OF THESE MESSENGERS THE **SECOND MORNING URINE** IS REQUIRED. FOR THIS PURPOSE ***biovis'*** OFFERS A UNIQUE **"URINE-SPOT" PROCEDURE**.

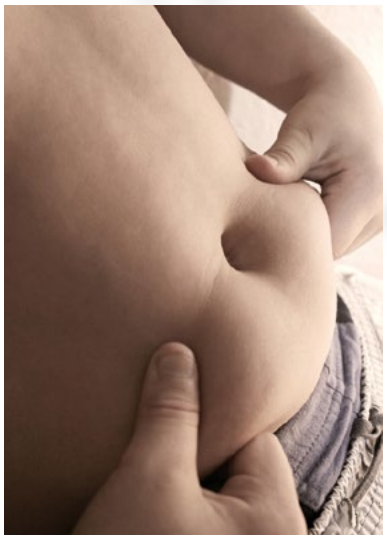
WHICH ONLY REQUIRES ONE DROP OF DRIED URINE TO DETERMINE ALL MENTIONED PARAMETERS (ADRENALIN, NORADRENALIN, DOPAMINE, SEROTONIN, GABA, AND GLUTAMIC ACID). THE SUBSTANCES ARE STABLE IN DRIED URINE FOR SEVERAL WEEKS AND CAN BE SAFELY TRANSPORTED.

THE CATECHOLAMINE VALUES ARE INCREASED IN CASE OF STRESS. IF THE PATIENT ALREADY SUFFERS FROM A BURN-OUT OR CHRONIC FATIGUE SYNDROME, THE MEASURING RESULTS ARE OFTEN BELOW NORMAL, AS THE ADRENAL GLAND AS WELL AS THE NEURONS HAVE BEEN EXHAUSTED BY PRODUCING THE MESSENGER OVER THE LONG STRESS DURATION.

Serotonin – Neurotransmitter of Great Importance in Case of Chronic Stress

Serotonin is an **important inhibiting neurotransmitter** – but that is by far not all. Serotonin is also the **precursor of melatonin**, the antagonist of cortisol and it plays a major role in many other diseases.

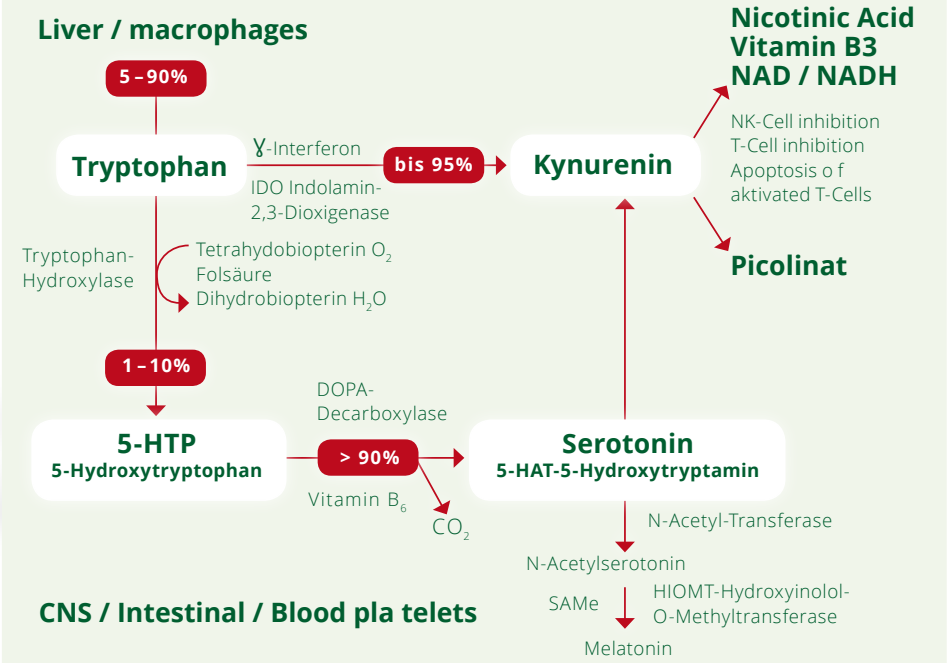
95% of the serotonin is produced **in the intestinal mucosa**. Further places of production are the central nervous system, liver and spleen. Starting substance of the serotonin synthesis is the **amino acid tryptophan**, which is transformed under the influence of Vitamin B6 and magnesium via the intermediate 5-hydroxy-tryptophan (5-HTP) to serotonin.



Serotonin has a **blood pressure regulating effect**, stimulates the vermicular movement of the intestines and controls the permeability of the mucosa and thereby the resorption of nutrients. Within the **nervous system** serotonin has relaxing, mood-elevating, sleep regulating, anxiolytic and antidepressant effects and positively influences on learning and memory as well as other cognitive abilities. Furthermore the control of our appetite is dependent on serotonin: High serotonin levels promote the feeling of satiety, low serotonin levels come along with ravenous hunger and may lead to **eating disorders**. Other diseases, which correlate with too low serotonin levels, are for example **adiposity, depressions, anxiety, sleeping disorders and migraine**. Stress has an influence on serotonin production. In case of acute stress the serotonin level may increase temporarily. If stress persists or becomes chronic the present serotonin level decreases for two reasons: For one more serotonin is needed and then the production is reduced. The reason for this is increased production of **pro-inflammatory cytokines**, like IL-6, TNF-α and INF-γ. Mainly the latter has a promoting effect on the enzyme indolamine-2.3-dioxyge- nase (IDO), which catalyses the transformation of tryptophan to **kynurenine** – a non-proteinogenic amino acid – causing an inhibition of the cellular immune response. This transformation may consume more than **95% of the present tryptophan**. In this case less than 5% remain for the serotonin synthesis. A deficiency is pre-programmed. In this case, however, not only chronic stress should be considered as possible cause for increased cytokine production. Also longer lasting inflam- mations in the body may cause serotonin deficiency – for example **parodontitis, chronic virus infections, auto-immune diseases, enteritis, food intolerances and not last a metabolic syndrome or central adiposity**, as the fatty tissue of the ab- domen (more precise the intra-abdominal adipocytes) also supplies considerable amounts of pro-inflammatory cytokines

Mit der **Diagnose eines Serotoninmangels** können Sie bei Ihren Patienten eine Ursache für vielfältige Fehlsteuerungen oder Krankheitssymptome aufzeigen – und sie einer gezielten Therapie zuführen.

Serotonin Deficiency...



THE SEROTONIN-DIAGNOSTICS:

THE NEW BLOOD-SPOT-TEST/ URINE-SPOT TEST

UP TO NOW IT WAS DIFFICULT TO DETERMINE RELIABLE SEROTONIN LEVELS AS THE STABILITY OF SEROTONIN IN BLOOD SERUM IS VERY LOW. THE SAMPLE WAS ONLY STABLE FOR AT THE MOST ONE AND A HALF DAY (CENTRIFUGED SERUM). TAKING INTO ACCOUNT THE TIME OF REGULAR SAMPLE SHIPPING THIS PRE- SENTS A CONSIDERABLE PROBLEM.

ONLY BIOVIS CAN OFFER NEW DEVELOPMENTS IN THIS FIELD, WHICH OVER- COME THESE DIFFICULTIES: THE BLOOD-SPOT TEST OR ALTERNATIVELY THE URI- NE-SPOT TEST. THEY ARE EASY TO HANDLE, COST-EFFECTIVE AND GU- ARANTEE HIGH SAMPLE STABILITY. FOR THIS TEST ONLY A LARGE DROP OF BLOOD RES- PECTIVELY A DROP OF URINE IS TRICKLED ON A SPECIALLY PRIMED TEST STRIP. AFTER LETTING IT DRY IN THE AIR FOR 1.5 TO 2 HOURS THE SAM- PLE CAN BE SHIPPED. PREPARED IN THIS MANNER THE SAMPLE WILL REMAIN STABLE FOR MORE THAN SIX MONTHS.

IN ADDITION THE BLOOD-SPOT METHOD MAKES IT POSSIBLE NOT TO TEST ONLY SEROTONIN BUT ALSO OTHER COMPONENTS OF THE SEROTONIN ME- TA- BOLISM. TRYPTOPHAN AS WELL AS KYNURENINE CAN BE DETERMINED. THIS PROVIDES FOR A DISTINCT LOCALISATION OF YOUR PATIENT'S DISOR- DERS WITHIN THE SEROTONIN SYNTHESIS.

Differential Diagnoses – Exhaustion, Burn-out or Chronic Fatigue Syndrom

Chronic stress may lead to a variety of exhaustion symptoms. As they may, however, also have other causes, a thorough differential diagnosis is important: Hypothyroidism, anaemia, mitochondrial diseases, mineral or vital substance deficiency or only a few possible examples for such causes. They should be reliably excluded before starting a stress therapy.

DIAGNOSTICS: DIFFERENTIAL DIAGNOSS AND EVALUATION OF THE CONSEQUENCES OF STRESS

DETAILED HAEMOGRAM, BLOOD SUGAR, CHOLESTEROL, LDL, HDL, TRIGLYCERIDES, HSCRP, HOMOCYSTEINE, TSH, POSSIBLY FT4/FT3, CO-ENZYME Q10, ZINC, SELENIUM, CITRULLIN AND OTHERS.

***biovis'* WILL GLADLY ADVISE YOU, WHICH FURTHER TESTS ARE RECOMMENDABLE AND IMPORTANT IN SPECIAL CASES. PLEASE DON'T HESITATE TO CALL US!**

And last but not least: Tips for Stress Therapies

If there are indications of chronic stress or even burn-out or chronic fatigue syndrome you have to look for the causes of stress together with the patient and then try to eliminate them. As this is not always possible, the patient should be encouraged to learn relaxing and **protection techniques**, which reduce his stress sensitivity. Furthermore the patient should be supplied with sufficient amounts of important amino acids. In case of catecholamine deficiency **phenylalanine** and/ or **tyrosine** have to be given together with **co-factors** important for synthesis (folic acid, calcium, iron, copper and vitamins C, B6, magnesium). If the magnesium level is too low, it is recommendable to give **tryptophan, vitamin B6, and magnesium**. In addition it is crucial to mention that a healthy diet is important, especially the consumption of healthy fats (important for cortisol and DHEA synthesis), lecithin and B- vitamins. Taking individual or complex micronutrient preparations cannot replace a healthy diet.

Stress-Diagnostics – Summary

CORTISOL UND DHEA(S)

CORTISOL – DIURNAL PROFILE (TEST SET FOR THREE SALIVA SAMPLES)
SAMPLING TIMES: 8 A.M., 2 AND 8 P.M.
POSSIBLY SUPPLEMENTED BY:
DHEA(S) DETERMINATION IN SALIVA SAMPLES OF 8 A.M. AND P.M.

CATECHOLAMINES, GABA, GLUTAMINE ACID

ADRENALINE, NORADRENALIN, DOPAMINE (SECOND MORNING URINE)
POSSIBLY SUPPLEMENTED BY GABA, GLUTAMINE ACID
FOR THIS PURPOSE ***biovis'*** OFFERS A UNIQUE "URINE-SPOT" TEST, WHICH MAKES POSSIBLE THE DETERMINATION OF ALL MENTIONED PARAMETERS WITH ONLY ONE DROP OF DRIED URINE. IN DRIED URINE THE SUBSTANCES REMAIN STABLE FOR SEVERAL WEEKS AND CAN SAFELY BI TRANSPORTED

PRECURSOR / CO-FACTOREN

AMINO ACIDS:	PHENYLALANINE, TYROSINE (EDTA BLOOD);
VITAMINS:	B6 FOLIC ACID (EDTA BLOOD); B12 (SERUM)
	C (HEPARIN, LIGHT-PROOF)
MINERALS:	CALCIUM, IRON AND COPPER (EDTA BLOOD, HEPARIN)

SEROTONIN/TRYPTOPHAN/KYNURENIN

SEROTONIN (BLOOD-SPOT TEST SET/ URINE-SPOT TEST)
PUT ONE LARGE DROP OF BLOOD ON THE FILTER STRIP AND LET IT DRY IN THE AIR.
AS AN ALTERNATIVE: SEROTONIN CAN ALSO BE DETERMINED IN CENTRIFUGED SERUM OR IN SECOND MORNING URINE.

CO-FACTOREN

VITAMINS: B6, FOLIC ACID (EDTA BLOOD)
MINERALS: MAGNESIUM (EDTA BLOOD, HEPARIN)

TRYPTOPHAN AND KYNURENINE

(BLOOD-SPOT TEST SET AS FOR SEROTONIN)
AS AN ALTERNATIVE: TRYPTOPHAN AND KYNURENINE CAN ALSO BE DETERMINED IN EDTA BLOOD OR BETTER EDTA PLASMA.

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