CHRONIC FATIGUE SYNDROME: A HOMOTOXICOLOGICAL PERSPECTIVE.

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CHRONIC FATIGUE SYNDROME:

INTRODUCTION:

Chronic fatigue syndrome is a complex constellation of symptoms that is now recognized by the World Health Organisation as a 'debilitating and distressing condition'. The syndrome is also the subject of intense research and debate throughout the medical world.
However if one view the syndrome in a Homotoxicological framework, one is confronted with a true environmental disease that exhausts all the body's defense mechanisms as described by Reckeweg to leave the organism defenceless to our modern lifestyle. One can also follow the progression through the 'six phase table' from suppressed reaction to the impregnation phase and as recent evidence suggests also to the neoplastic phase.

Let's look at the evidence for this syndrome as presented by conventional medicine.

1.NOMENCLATURE:

Chronic Fatigue syndrome has been rightly called the disease of a thousand names because as each new outbreak has been described a new name was added.(Jenkins, R 1992)

Sir Richard Manning as far back as 1750 observed a post-infectious disorder he called 'febricula'. Since then it has been called Atypical polio, Royal Free disease (UK), endemic neuromyasthenia (USA), and Tapanui flu(New Zealand).

Later it was called myalgic encephalomeylitis or ME(UK) and Chronic Ebstein Barr (USA).The media term 'Yuppy flu' is derogatory and incorrect and should be avoided.

Currently it is referred to as Post-viral fatigue syndrome in the
UK (PVFS) and to Chronic fatigue and immune dysfunction syndrome(CFIDS) in the USA.

Mostly it is called Chronic Fatigue Syndrome (CFS) as this implies no particular cause. This term will be used here.

Patients who do not fulfil the diagnostic criteria but have significant fatigue are being classified as having Idiopathic Fatigue or just Chronic Fatigue(CF).(Shepherd 1994)

2.PREVALENCE:

It is difficult to estimate correct figures for CFS as a large number of other patients may currently be included from poor diagnostic procedures.

Prevalence is estimated at 1:1000 of the population in the UK. Recent American studies put prevalence at 37.1:100000(Lloyd 1992) and 98-267:100000. In the same study the prevalence for CF was 2414-6588:100000.(Buchwald et.al.1994) Although the condition can affect the very young and the very old the incidence is the highest in the age group 20-40 years and there is a slight female predominance.Teachers and health care professionals are more often afflicted.

3.DIAGNOSIS:

a.Criteria:

For many years researchers have been searching for the 'footprint in the sand', the one laboratory marker that would distinguish
CFS from other diseases, but until now this has been elusive.

Therefore the Centre of disease control and prevention in Atlanta asked Holmes to develop a set of criteria to identify these patients for research purposes.(Holmes 1988) To complicate matters further a similar but different set of criteria is used in the UK (so-called Oxford criteria) and Australia developed yet another set of criteria. TABLE 1,2,AND 3.
However, a recent study comparing these case definitions found them accurate to define patients diagnosed by one of the other sets.(Bates et al 1994)

Apart from these criteria other symptoms are observed in practice that can support the diagnosis of CFS.

. Autonomic hyperactivity like palpitations and urinary frequency. Hypotension.

. A high incidence of irritable bowel syndrome symptoms.

.Intolerance to toxins like alcohol, allopathic drugs and environmental toxins.

.A history of allergy and frequent infections in the pre-morbid state. This is of course often associated with the frequent use of antibiotics and antihistamines.

.Symptoms related to the connective tissue like arthralgia and oedema.

.Symptoms related to the hypothalamic pituitary axis like menstrual disturbances and poor temperature control.

b.Laboratory studies:

As a baseline one should check liver, thyroid and renal function together with a full blood count. Serum folate and Vitamin B12 levels should be done as well. ANF testing is important as the syndrome may resemble early Lupus or other auto-immune disease. T-cell subsets are usually done to determine immune dysfunction. (see below). HIV testing is only neccesary if there is a suspiciious history. The differential diagnoses of CFS is of course very big but with a good history most possibilities can be eliminated.(Table 4.)

4.PATHOGENESIS:

Through immunological, metabolic, viral and environmental studies most allopathic practitioners agree that the cause of CFS is multifactorial.

a. Evidence of immune dysfunction:

A large number of subtle abnormalities have been found in patients with CFS but as the subjects were not controlled for severity and duration of illness it is difficult to draw definite conclusions from it.(Buchwald 1992).
The most consistent finding is that of a decreased Natural Killer cell function. More and more studies suggest a state of immune activation and it seems that this may be in response to a viral infection. Whether it is a reactivated virus or an initiating virus, is not clear. The most common abnormalities found are a decrease in CD8+ cells with the marker CD11b+, thus T-suppressor cells. An increase in the activation markers CD38+ and HLA-DR suggest activation of a line of cytotoxic cells. This pattern is not seen in people who are depressed or in normal family members of the subjects and seem to be peculiar to patients with CFS.

A similar pattern of cell activation is seen in acute viral infections but this return to normal within two weeks after the infection. In acute viral infections there is a rise in CD11b populations and Natural killer cell activity instead of a reduction as seen in CFS.(Baker et.al.1994)(Levy 1994).

Evidence for immune activation has been seen in another study where 80% of subjects with CFS had elevated Angiotensin converting enzyme (ACE) levels compared with 9.4% in non-endemic controls.(Liebermann and Bell 1993)
Raised levels of cytokines (Il 1, Il 6,and TNF) were found by various groups and postulated as the mechanism responsible for the symptoms of CFS.(Lloyd 1994) (Patarca et a 1994)

Certain cytokines act as neurotransmitters once they cross the blood brain barrier and can cause changes in mood and cognitive function. Some (Interleukin 1 and 6)influences the hypothalamic pituitary axis.(Reichlin 1993) (Fig 1)

A number of these patients develop a low grade of auto-immunity and there is an overlap with certain known auto-immune disease like Sjogrens syndrome.(Calabrese et al 1994). The significance of this is unknown although two mechanisms are possible. The population of T-suppressor cells play a major role in the tolerance of the immune system towards itself (Yoshida and Gershwin 1993).Secondly, through toxins damaging cell membranes large amounts of self proteins may be exposed to the immune .system before the scavenging cells can clear it up, causing tolerance to break down.

b.Viral studies:

The role of different viruses in CFS has been the subject of intense reasearch.
Herpesviruses,Enteroviruses and Retroviruses have been investigated.(De Freitas 1992) (Martin 1992)(Komaroff 1992) (Levy 1994)
Although both Ebstein Barr virus and Herpes simplex virus 6 titres are elevated often this is thought to represent viral reactivation in the face of a compromised immune system as discussed above.
The role of the Coxsackie B virus has been emphasized in the UK.(Gow et al. 1994)
Antibodies have been detected and viral RNA was been found in the muscles of certain subjects.These viral particles however have also been found in the muscles of patients with other neuromuscular diseases.

This suggests that Enteroviruses do not contribute to the muscle pathology as such but the theory is that the Coxsackie virus imbeds itself in damage muscle. It cannot be excluded as an initiating event in CFS however. (Gow 1994)

Retroviruses have been investigated but is generally believed to play no role in the pathogenesis of CFS.(Heneine et el 1994)(Levy 1994)

A few researchers have postulated the theory of a 'hit and run' viral infection that might trigger the process, is then eliminated ,but leaves the immune system in an activated state.
This is supported by the finding of upregulation of the 2-5A synthetase/RNase antiviral pathway in patients with CFS.(Shuhadolnik et al 1994)

c.Neuro-endocrine and Neurotransmitter studies:

The new discipline of psycho-neuro-endocrine-immunology has been a popular field of research in the latter years. Also, in CFS there is a link between these various systems.(Fig 1)

Hypothalamus-pituitary-axis studies suggest an upregulation of serotonergic pathways in CFS. Also, the levels of metabolites of the mono-amines is reduced in the plasma suggesting a deficiency.
Abnormal arginine vasopressin secretion and abnormal control of water metabolism have been shown.(Bakheit 1993) Various studies in the UK and Italy showed an abnormal secretion of basal cortisol and a low level of growth hormone in these patients. This may be as the result of a blunted response to CRH and may further contribute to the immune activation as well to the adipositas and hypoglycaemia observed in a large group suffering from this syndrome.(Dinan and Majeed 1994) (Pizzigallo et al 1994).

d.Metabolic abnormalities:

Several abnormalities in mitochondrial function have been demonstrated, notably acylcarnitine deficiency, a substance that plays a role in energy production and the modulation of Co-enzyme A.(Kuratsane et al 1994). The mitochondria itself are pleomorphic with proliferated cristae. (Behan et al 1994). A defect in oxidative metabolism was found(Barnes et al 1993) where CFS patients had reduced cellular concentrations of ATP.

e.Environmental research:

More direct links are found between CFS and toxin exposure such as organophosphates (Shepherd 1993) and so called sick buildings.(Chester and Levine 1994) Many other accounts of toxins causing similar symptoms as in CFS have been documented. (Behan and Haniffah 1994)
The effect of overloading the detoxication systems of the liver has been well documented by Dr. Sherry Rogers in her book: 'Tired or Toxic.' (Rogers 1990). This can be explained with the Aldehyde Pathway as example. (Fig 2) All alcohols are detoxified via this pathway including formaldehyde and the hydrocarbons. The process is facilitated via a series of enzymes that work at a certain rate and are dependent on certain co-factors (example Zinc, Molybdenum and Selenium) for their function. Certain of these intermediate substances like acetaldehyde is highly toxic. Furthermore, if the system becomes overloaded, the homotoxins may be shunted into other pathways with equally toxic byproducts, eg. alcohol is shunted into chloral hydrate. The latter substance is commonly use to sedate children for invasive procedures and cause fatigue in adults. Should the system get overloaded or the co-factors for the detoxifing enzymes are not present, a backlog occurs with various results. (Fig 3.)
These toxic substances may also form highly reactive superoxides that may damage cell membranes, proteins ect. This will be enhanced if there is a shortage of anti-oxidants like Beta-carotene, Vit.C, Vit.E, and glutathione.(Selenium)

f.Structural and functional abnormalities in the brain:

On MRI-scanning of the brain 78% of patients studied were found to have areas of high signal intensity in the sub-cortical areas consistent with demyelination or oedema.(Buchwald et al 1992)

Recently brain perfusion scans with 99m Tc HMPAO or so-called SPECT scans have received a lot of attention as they suggest hypoperfusion in some areas of the brain, particularly the hypothalamus and brain stem. This pattern is induced by

exercise and differs from that seen in patients with depression.(Costa et al 1992 and 1994.)

5.CFS FROM A HOMOTOXICOLOGICAL PERSPECTIVE:

According to Reckeweg disease is an appropriate attempt of the body to rid itself from toxins. It is an expression of the body's defense mechanisms attempting to eliminate or compensate for damage cause by exogenous and endogenous homotxins.

To do this it engages the greater defense system consisting of the Reticuloendothelial system and it's components, the liver, the hypothalamic-pituitary axis ,the neural reflexes and the connective tissues.
If the body is unsuccessful, the toxins will be driven deeper into the body or on the Six phase chart to the right eventually through the biological cut into the cellular phases.

Allopathic medicine has in recent years recognized the interaction of all these systems in the discipline of neuro-endocrine-immunology.(Reichlin 1993)

As we can see from current research we are dealing with a syndrome where the body is unsuccessfully trying to rid itself from toxins whether viral or environmental.

We have seen evidence for a dysfunctional, activated immune system secreting neurohumeral substances to cause inflammation.

We have seen evidence for an overloaded liver not coping with the amount of toxins it has to eliminate by that shunting them into the blood stream and ultimately into the connective and fatty tissue(Deposition phase)and the brain where it may cause demyelination(Degeneration phase).

The patients with CFS have marked autonomic dysfunction with low blood pressure, palpitations etc. In practice one often sees neurodermatitis developing in these patients-another attempt of the autonomic nervous system trying to rid the body of toxins.(Reaction Phase).

The arthralgia and muscle aches suggest the connective tissue as the battle ground in this war between toxin and immune system.

The evidence for a disordered Hypothalamic- pituitary- adrenal axis is clear.

We have seen evidence for a disruption in oxidative metabolism putting this syndrome to the left of the biological cut in the impregnation phase.

Recent studies suggest a higher incidence of brain tumours in the
patients who contracted CFS in the Lake Tahoe area of the United States.(Levine et al 1994) If this is indeed the case, we have seen the ultimate shift in the Six Phase table to neoplasm.

6.PROPOSED MECHANISM OF PATHOAETIOLOGY:

a.Conventional thinking:

This is represented by Fig.4.(Shepherd 1994)

b.Holistic model:

Like with any other disease one need three factors to contract CFS: a genetic predisposition, an environment that will proliferate this predisposition and thirdly a trigger to start the process.

i.Genetic Predisposition:

These are the tendencies towards disease that we inherit from our parents. In CFS recent studies suggest that certain HLA allelles may be risk factors in the development of CFS.
We know that the efficiency of our detoxifying enzymes in the liver(Fast versus slow acetylators) and probably the efficiency of our immune system is inherited.

Family studies of victims of CFS suggest a higher than normal incidence of auto-immune disease, allergy and cancer.

ii.Environment:

It goes without saying that our modern environment poses a greater than ever threat to the organism. We live with toxic substances in our food, our homes, our air.

The body becomes overloaded and if the vital co-factors to the detoxifying and energy forming enzymes like vitamins and minerals are missing the scene is set for disaster. The quality of our food and ground water is extremely poor in these nutrients. Take a typical CFS patient who had allergies and as a child. This would have been most likely suppressed with anti-histamines and cortisone. The patient then shifts towards chronic sinusitis and asthma. This is treated with frequent antibiotics and more cortisone. The next step is bowel dysbiosis with yeast overgrowth.

Food sensitivity then becomes a problem as the good bacteria no longer form a barrier against toxins. the liver gets overloaded, shunt toxins like Acetaldehyde (FIG 1 and 2) or it 's more lethal byproducts into the blood stream where it damage protein structures,cell membranes. The immune system being vulnerable gets damaged.

iii.The trigger:

This could be anything from a flu-like illness to a stressful situation to a chemical exposure(like putting flea powder on the dog or moving into a sick building). Rather than being an initiating event this is the straw that breaks the camel's back and we have a patient who can't work, sleep or play. Most CFS patients report not having felt well for years till some event that really made them sick.

7.MANAGEMENT OF THE CFS PATIENT:

CFS patients form a heterogenous group in various stages and duration of disease. While allopathic medicine has no means at this stage to classify this, the homotoxicologist can, with the help of the' six phase table' work out a comprehensive treatment programme for each patient.

a.History:

A good homotoxicological history should be elicited bearing in mind that the problem is the sum of many environmental onslaughts over many years including events that may be foci perpetuating the problem or will prevent cure until eliminated.

b.Diagnosis:

Apart from the diagnosis on criteria and the basic laboratory screen as described earlier, the homotoxicologist should try to classify the patient on the six phase table.

This may include measures such as an MRI scan of the brain to see if demyelination is present,and to exclude Multiple sclerosis(Which can present with the same symptoms)or to look for neoplasm.

Other biological methods such as Elecroacupuncture testing are invaluable in this syndrome to document organ involvement, intoxication with, for example, heavy metals or to delineate triggers and foci.

c.Treatment:

The treatment of CFS is holistic.It is a syndrome with a plethora of symptoms and if we treat each one with an 'anti-'drug we shall make the sick sicker!.
There are various allopathic regimes, mostly based on symptoms that won't be discussed here.Interested readers will find a review in the "Guidelines for the care of patients" by Charles Shepherd. (Shepherd 1994)

i.General:

From the above it is clear that we are dealing with a patient that has exhausted his greater defense system apart from the immune system that is overactive and raging it's own war in

the connective tissues and brain. We have an organism that is unresponsive and walking a pathway to maybe neoplastic proliferation. The major principles of homotoxicology namely to induce regressive vicariation through inducing a reaction and supporting the detoxifying organs hold true.

The environment of the patient should be adapted to be as toxin free as possible. Treatment of bowel dysbiosis with diet and sanitation should be started as first line treatment. There are various regimes described. A basic vitamin, mineral and anti-oxidant supplement should be given to prime the detoxifying and phosphorylating enzymes.

Stressful situations should be avoided and if the patient is sick enough they should be booked off work.Just explaining the situation to the patient who has been shunted from one doctor to another and finally to the psychiatrist is of tremendous value.

ii.Specific treatment:

Aim of treatment is as follows:

.To stimulate oxidative metabolism.

.To open the pathways of detoxication through the connective tissue, liver and kidneys.

.To modulate and purify the dysfunctional immune system.

.To regenerate organs and systems affected.

.To find and treat via nosodes foci and old toxins preventing a cure.

.To treat symptoms supportively till the above measures take effect

Auto sanguis step therapy offers a quick and elegant way of treatment.

I often treat with Co-enzyme comp., Ubichinon comp. initially daily, then three times a week together with Carnitine 500mg three times a day on an ongoing basis to restore oxidative metabolism. Nux Vomica hommacord is added to help in the treatment of dysbiosis.This is done as oral treatment at home.

As auto sanguis step therapy:

Step 1: Symptomatic:

Traumeel (pain etc.)
Vertigoheel(dizziness)
Spigelon(migraine etc.)
Selenium homaccord(concentration)

Step 2: Terrain:

Lymphomyosot(Drainage of the connective tissue)
Hepar comp. (Liver drainage)
Solidago.(Kidney function)
Galium heel(Immune system)
Engystol (Anti-viral)
Co-enzyme (oxidative metabolism)

Step 3: Organ regeneration:

Cerebrum Comp.(blood supply to the brain)

Tonsilla comp.(regeneration of the immune system, hypothalamus and adrenals.)

Hepar suis. (Liver regeneration)

(Recently, a report was published where CFS patients were treated with a porcine liver extract with good results.- ? Suis organ therapy! (Steinbach et al 1994)

Glandula suprarenalis injeel.(regeneration of the adrenals)

Cerebrum suis injeel(in demyelination)

Step 4: Nosodes:

These should be chosen individually, except Psorinoheel.(for genetic tendency to develop CFS)
Grippe nosode often indicated .
Cortisone nosode if indicated.

Others on grounds of history.

The course is started with Step one and two for two to three weeks after which the organ prepararations are added for tree to four weeks.
The nosodes are added on a two weekly basis alternating if more than one is indicated.

If no regressive vicariation is achieved, the course should be repeated, if still no reaction a urgent search for Foci must be made for example with EAV.

Teeth sanitation plays an important role in the treatment as metal fillings or dead teeth often represent the focus preventing cure.

If a reaction occurs, these symptoms must be welcomed and supported. These patients often have not had a cold or a flu-like illness for years and it is a good sign when the system responds with an excretion phase event.

Apart from the above also China Hommacord drops and Hormeel drops can be given orally, especially for female patients who feels worse during their menses.

iii.Other measures:

Own blood therapy:

Own blood therapy in an oral form is useful to stimulate the immune system in the bowel wall also providing a very specific nosode for the patient.The treatment should be started with a higher dilution as we are dealing with an overactive immune system.

Acupuncture:

An invaluable method to restore energy flow and to control pain.

Ozone and Oxygen Therapy:

Again helpful to modulate the immune system and to help cellular respiration. However one must be sure that the patient is not deficient in anti-oxidants.

14.

Supportive psychotherapy:

Of value to teach the patient to pace him or herself and to help family relationships in view of the chronicity of the syndrome.The concept of 'the burden of illness' has received attention lately and seem to respond to behavioural manipulation. (Antoni et al 1994)

Bach Flower remedies

An important part of treatment in adjunct with the above.

CONCLUSION:

Chronic fatigue syndrome is a puzzling syndrome with high morbidity. Many work hours are lost and family dynamics impaired through the debilitating symptom complex.

However, if one view CFS in a Homotoxicological framework one sees a syndrome that can be explained according to the theory of Reckeweg's principles of disease. The syndrome can be treated accordingly to invoke regressive vicariation towards the right of the 'Six phase table' and often to cure bring about a complete cure.

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Eighteen pages with referances. (next page)

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TABLE 1

Oxford Criteria

Chronic fatigue syndrome (CFS)

(a) A syndrome characterized by fatigue as the principal symptom.
(b) A syndrome of definite onset that is not life long.
(c) The fatigue is severe, disabling, and affects physical and mental functioning.
(d) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.
(e) Other symptoms may be present, particularly myalgia, mood and sleep disturbance.
(f) Certain patients should be excluded from the definition
They include:
(i) Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether he medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.
(ii) Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion

Post-infectious fatigue syndrome (PIFS)

This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of actiological significance is a topic for research). To meet research criteria for PIFS patients must:
(i) fulfil criteria for CFS as defined above and
(ii) should also fulfil the following additional criteria:
(a) There is definite evidence of infection at onset or presentation (a patient's self- report is unlikely to be sufficiently reliable).
(b) The syndrome is present for a minimum of 6 months after onset of infection.
(c) The infection has been corroborated by laboratory evidence.

FROM: SHEPHERD CB, 1994.

TABLE 2

CDC criteria

Major criteria	Symptom criteria	Physical criteria
1. Fatigue for six months or more	1. Chills	1. Fever
2. Exclusion of organic or psychiatric disorders which cause similar symptoms	2. Sore throat	2. Pharyngitis
	3. Muscle weakness	3. Lymphadenopathy
	4. Painful lymph glands	
	5. Myalgia	
	6. Post-exercise fatigue	
	7. Headache	
	8. Arthralgia	
	9. Disorder of higher cerebral function	
	11. Sleep Disturbance	
	12. Acute or subacute onset	

(In order for a positive diagnosis of CFS to be made, two major criteria must be present, together with at least six symptoms and two physical criteria, or eight or more of the symptom criteria.)

TABLE 3

Australian criteria

(1) Generalised, chronic persisting or relapsing fatigue, exacerbated by very minor exercise, causing significant disruption of usual daily activities, and of over six months' duration; and

(2) neuropsychiatric dysfunction including impairment of concentration (difficulty in completing mental tasks that were easily accomplished before onset of syndrome) and/or onset of short term memory impairment; and/or

(3) abnormal cell-mediated immunity indicated by reduction in absolute count of T8 and/or T4 lymphocyte subsets, and/or cutaneous anergy.

(4) In addition, the following indings are supportive: myalgia, arthralgia, headaches, depression, tinnitus, paraesthesiae, and sleep disturbance persistent over six months with no other cause, and lymphadenopathy, localised muscle tenderness and pharyngitis (on two or more occasions after the initial illness)

FROM: SHEPHERD 1994

TABLE 4

Differential Diagnosis

Although extensive and elaborate investigations are seldom required other causes of chronic fatigue must be considered where the history is atypical. Also remember that "new" symptoms should not be automatically ascribed to ME/PVFS.

CARDIOVASCULAR
Valve disease

ENDOCRINE/METABOLIC
Addison's disease
Fluid Retention Syndrome
Hypothyroidism
Pituitary tumour
Thyrotoxicosis

Hypercalcaemia
Hyponatraemia

GASTROINTESTINAL
Coeliac disease
Crohn's disease
Food allergy
Irritable bowel syndrome

HAEMATOLOGICAL
Anaemia

INFECTIONS
Brucellosis
Giardia
Hepatitis B or C
HIV
Leptospirosis hardjo
Lyme disease
Parvovirus
Post-polio syndrome
Toxocara (children)
Toxoplasmosis

MALIGNANCY
Hodgkin's lymphoma

NEUROMUSCULAR
Multiple sclerosis
Myasthenia gravis
Parkinson's disease
Rare myopathies

PSYCHIATRIC
Anxiety +/- hyperventilation
Depression
Post traumatic stress
Somatisation

RESPIRATORY
Sarcoidosis
Tuberculosis

RHEUMATOLOGICAL
Fibromyalgia
Sjögren's syndrome
Systemic lupus erythematosus

MISCELLANEOUS
Alcohol
Allergies
Organophosphate pesticides
Sick building syndrome
Sleep apnoea
Narcolepsy

From: Shepherd 1994

Neuro-Endocrine-Immune Interactions

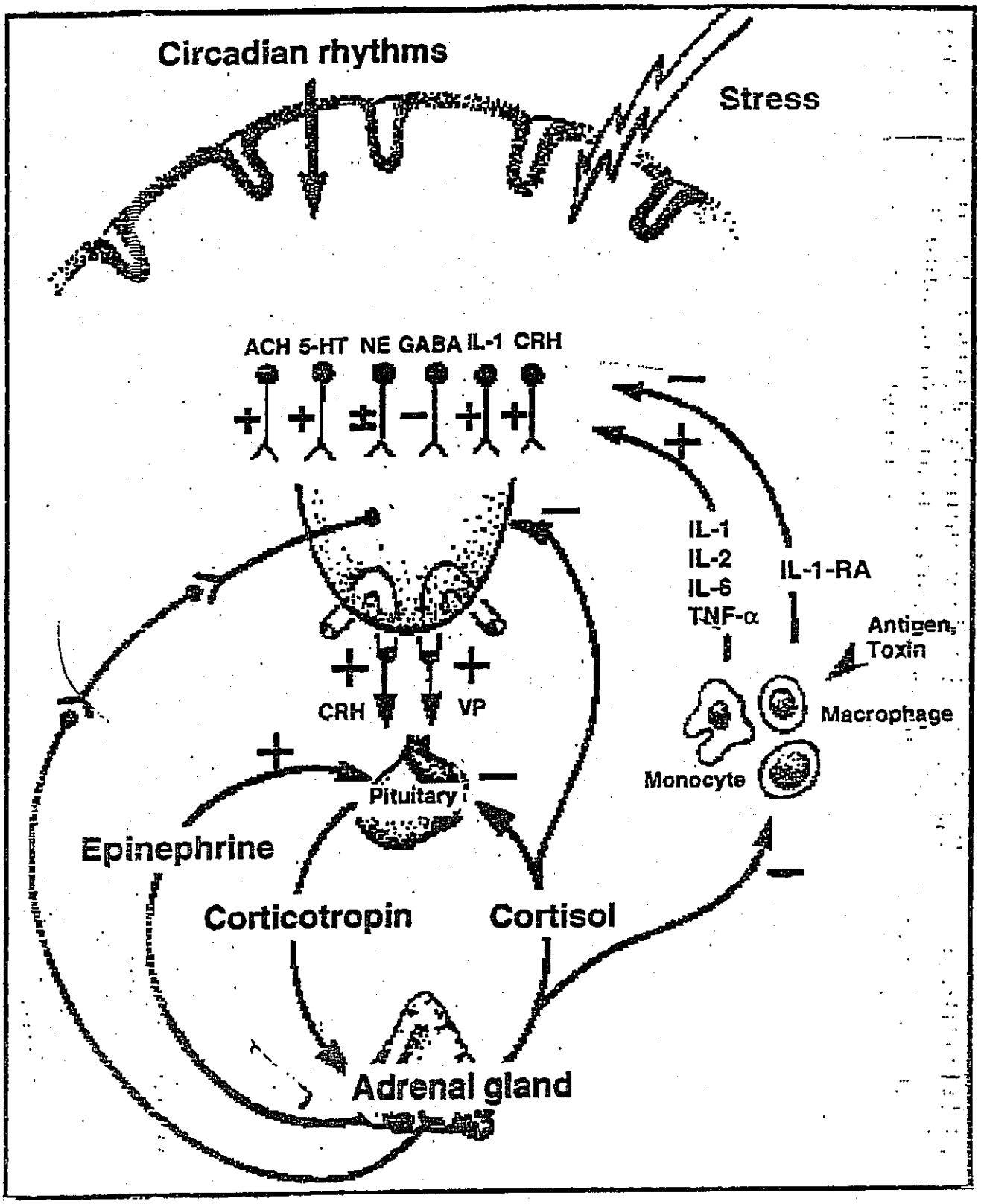

Fig 1. From: Reichlin 1994.

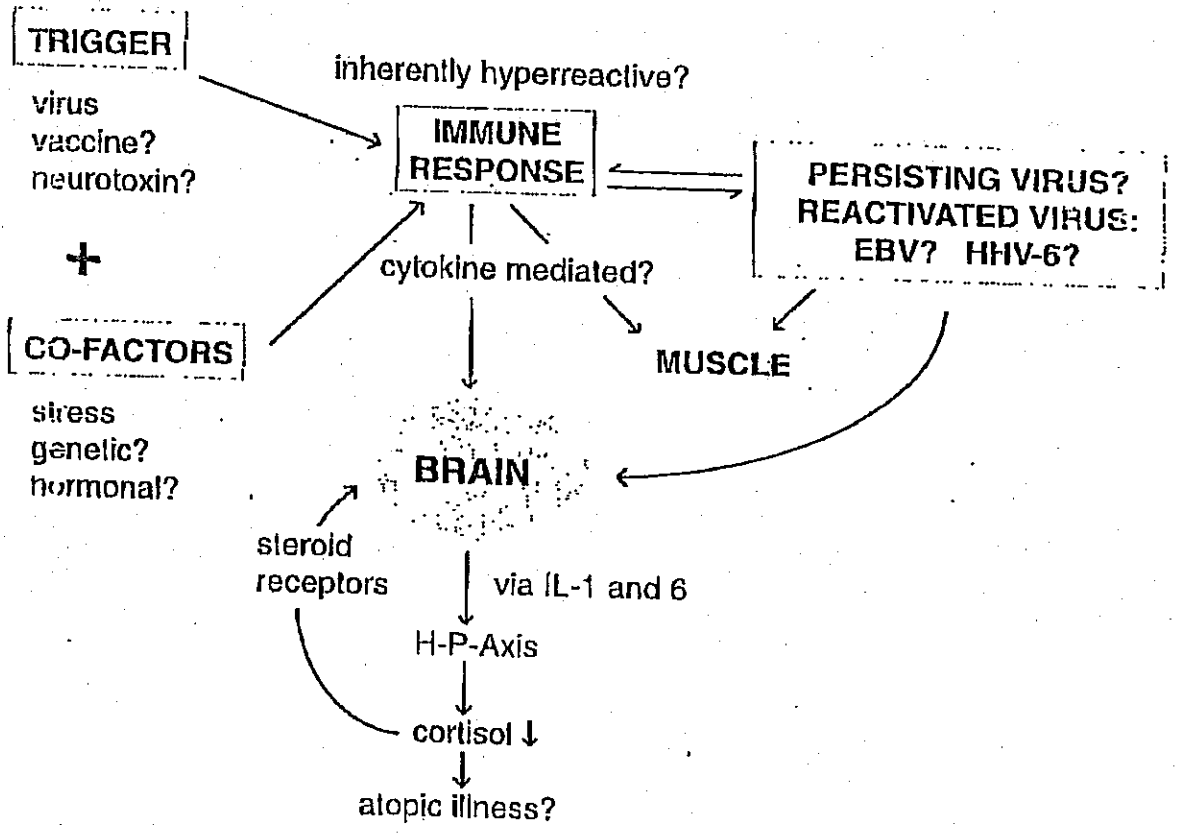

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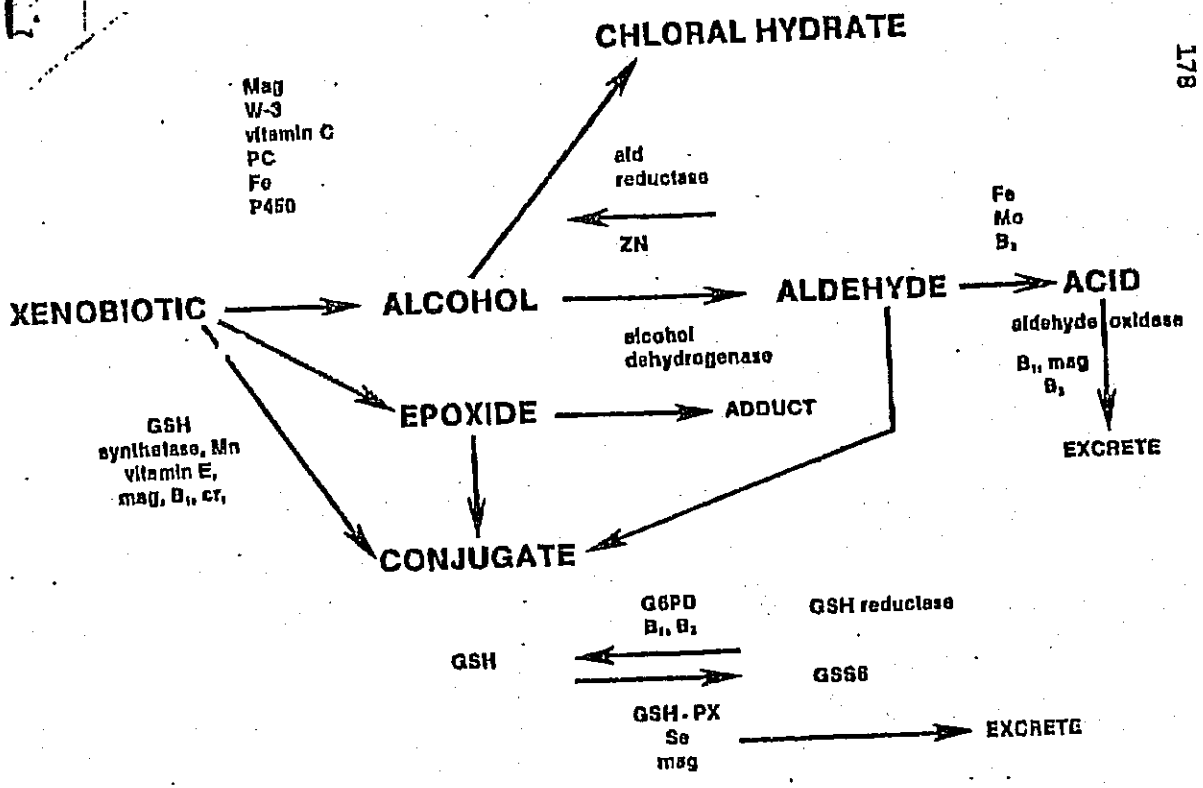
Fig 4 From: Shepherd 1994

Fig. 2.1



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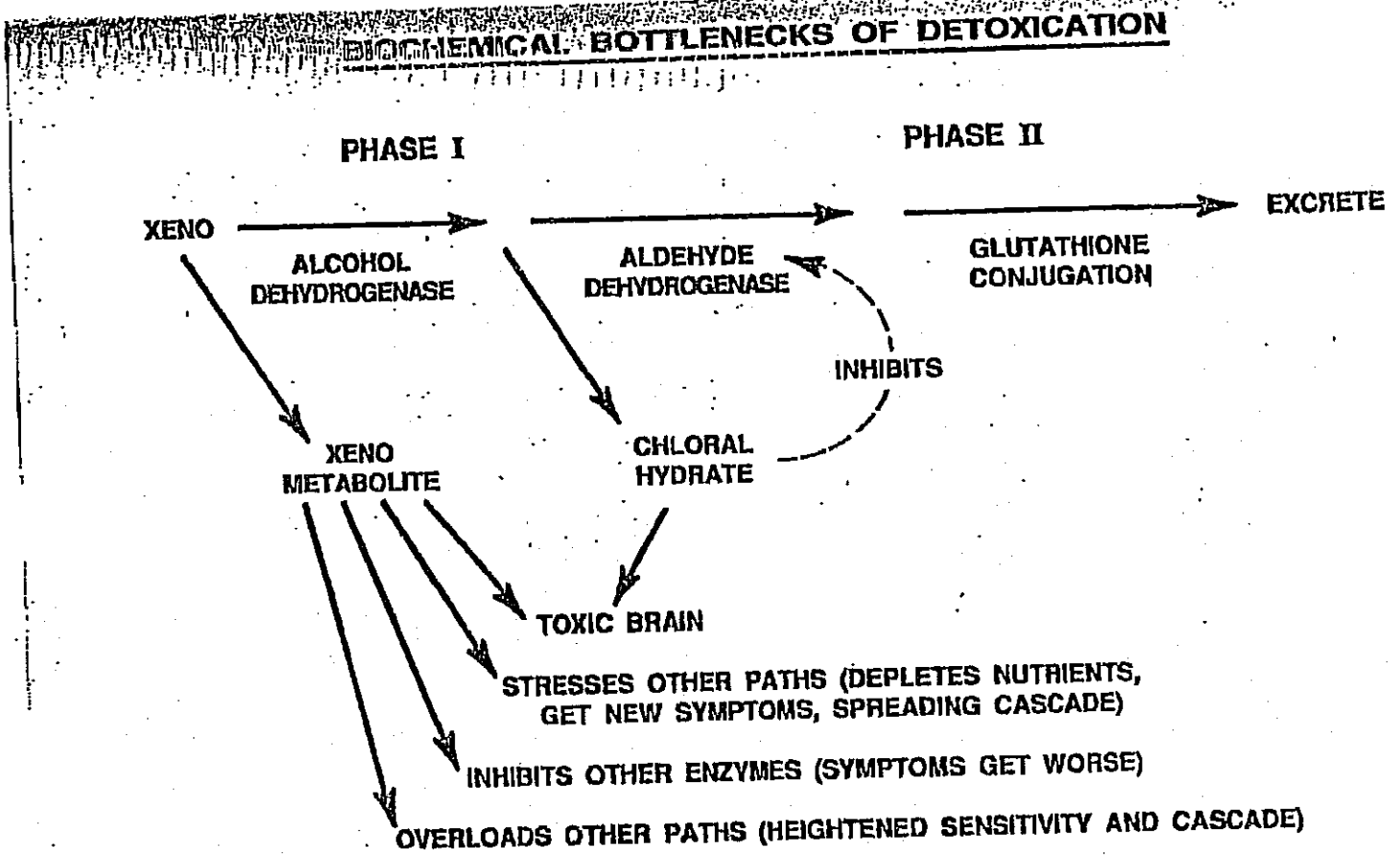
From Rogers: 1990

fig 3.



From Rogers 1990