The Unknown Mechanism of the Overtraining Syndrome
Clues from Depression and Psychoneuroimmunology

Lawrence E. Armstrong and Jaci L. VanHeest
Human Performance Laboratory, Department of Kinesiology, University of Connecticut, Storrs, Connecticut, USA

Abstract
When prolonged, excessive training stresses are applied concurrent with inadequate recovery, performance decrements and chronic maladaptations occur. Known as the overtraining syndrome (OTS), this complex condition afflicts a large percentage of athletes at least once during their careers. There is no objective biomarker for OTS and the underlying mechanism is unknown. However, it is
not widely recognised that OTS and clinical depression [e.g. major depression (MD)] involve remarkably similar signs and symptoms, brain structures, neurotransmitters, endocrine pathways and immune responses. We propose that OTS and MD have similar aetiologies. Our examination of numerous shared characteristics offers insights into the mechanism of OTS and encourages testable experimental hypotheses. Novel recommendations are proposed for the treatment of overtrained athletes with antidepressant medications, and guidelines are provided for psychological counselling.

The goals of training in sport are to enhance and optimise performance. When the daily intensity, duration and total workload of exercise is appropriate, positive physiological adaptations occur in muscle and other tissues, and physical performance typically improves. When prolonged, excessive training stresses are applied concurrent with inadequate recovery, many of the positive physiological changes associated with physical training are reversed with overtraining. Chronic maladaptations and performance decrements occur. Throughout the twentieth century, many names have been given to this chronic maladaptive state (e.g. underperformance syndrome, sports fatigue syndrome), but presently the term overtraining syndrome (OTS) is used in this manuscript.

In simple recognition of the need for adequate recovery, distance runners in the US have alternated hard and easy training days since this concept was popularised in the 1970s. During strenuous resistance training, a similar means of allowing recovery is accomplished by performing upper and lower body exercises on alternating days. Periodicity of training is widely accepted as the most reliable means to elicit optimal performance while minimising the likelihood of decrements. The macro-, meso- and microcycles of this regimen allow regeneration to occur following systemic (e.g. musculoskeletal, neuroendocrine) overload that is sometimes excessive. Yet, despite elaborate annual periodisation programmes for resistance and endurance athletes, even the most experienced coaches admit that they cannot predict which team members will experience performance decrements. This is disconcerting for coaches and athletes because OTS affects a substantial percentage of athletes involved in intense training programmes. Studies have reported that the signs and symptoms (SAS) of OTS appeared in >60% of distance runners during their athletic careers,>50% of professional soccer players during a 5-month competitive season, and 33% of basketball players participating in a 6-week training camp.

Although several theories now exist, scientists acknowledge that the mechanism of OTS remains unknown. Few data from controlled studies exist because: (i) training that is aimed at reducing function is self-contradictory; (ii) the motivation to train at a level that induces OTS usually depends upon foreseeable competitive goals; and (iii) an athlete who participates in such an investigation could conceivably lose one season of training – a price that few are willing to pay.

In considering the aetiology of OTS, we recognised that the SAS of OTS were similar to those of depression, by consulting previous publications. Subsequently, we recognised that OTS and depression share neuroendocrine pathways and brain structures that restore homeostasis in response to stressors (e.g. environmental and psychological factors that disturb homeostasis). Based upon the extensive literature regarding depression, the purpose of this review is to propose a novel perspective of OTS and to propose potential treatments, where none currently exist.

1. The Training Continuum

Figure 1 presents the continuum of training states that athletes may experience within a competitive season or periodised training cycle. These phases of training (see rectangles) range from undertraining, during the period between competitive seasons...
or during active rest, to overtraining which induces maladaptations and diminished competitive performance. This figure emphasises the fact that a successful training regimen must involve not only ample overload (e.g. the zone between the dashed lines), but also must avoid the dreaded combination of excessive overload plus inadequate recovery.

The outcomes in figure 1 emphasise two additional facts: (i) that adjoining levels of training (see rectangles) can result in similar outcomes (see ovals), depending on the nature of training and the blend of exercise stress with recovery and regeneration; and (ii) athletes at their peak (see * symbol) are also on the threshold of overtraining (see dashed line at right). Indeed, the border between optimal performance and a performance impairment due to overtraining is subtle; this applies especially to physiological and biochemical factors. The apparent vagueness surrounding OTS is further complicated by the fact that the clinical features are varied from one individual to the next, nonspecific, anecdotal and numerous. No single test is diagnostic.

The following definitions are provided, in concert with figure 1, to clarify the vocabulary and meanings used in the present review. Overload refers to a planned, systematic, progressive increase in training stimuli that is required for improvements in strength, power and endurance. Over-reaching refers to training that involves a brief period of overload, with inadequate recovery, that exceeds the athlete’s adaptive capacity. This process involves a temporary performance decrement lasting from several days to several weeks. Some authorities view over-reaching as a deliberate attempt to induce optimal performance; others view it as an unplanned, undesirable outcome of strenuous training. If a plateau or decrease in performance is reversed within a few days or weeks, and is followed by performance that exceeds the level previously experienced, over-reaching is involved. Although this term has been used as a synonym for short-term overtraining, the present review disregards this distinction. Furthermore, the present review emphasises chronic performance decrements and considers these to occur only with overtraining (figure 1). Overtraining exceeds over-reaching and results in frank physiological maladaptation(s) and chronically reduced exercise performance. It proceeds from imbalances between training and recovery, exercise and exercise capacity, stress and stress tolerance; training exceeds recovery, exercise exceeds one’s capacity, and stressors exceed one’s stress tolerance.

Fig. 1. The continuum of training states that an athlete may experience within a competitive season (e.g. periodised training mesocycle). (a) During the period between competitive seasons or during periods of active rest. (b) Peak performance occurring in training and competition. OTS = overtraining syndrome; * indicates athletes at their peak performance.
The topic of this review, OTS, is a set of persistent physical and psychological symptoms (table I) that occur subsequent to prolonged application of heavy training loads. The critical OTS diagnostic factor is a chronic decrease in performance, not simply the existence of SAS. The reader should note that overtraining is a process and OTS is the attendant outcome. Because no definitive mechanism has been identified, considerable disagreement exists in the use of vocabulary and the meaning of terms that describe OTS in the scientific and clinical literature. Synonyms for OTS include staleness, overwork, stagnation, chronic fatigue, overfatigue, overstrain, burnout and overtraining.\[9,13\] Although as little as 10 days of increased training may result in over-reaching,\[14\] complete recovery from OTS requires from several weeks to several months.\[15\]

2. The Complexities of Overtraining Syndrome (OTS)

A remarkable number of SAS have been associated with OTS in numerous sports. In fact, Fry et al.\[17\] listed over 90 in their 1991 review of OTS. Clearly, such a large list makes diagnosis of OTS difficult for the coach and sports medicine physician because the best diagnostic criteria are not obvious. In fact, the clinical assessment of OTS typically involves a diagnosis by exclusion, in which all other likely conditions are eliminated.\[18\]

Four additional matters complicate simple recognition of OTS. First, there may be considerable inter-individual variability with regard to the development of overtraining, on the same athletic team.\[3,10,11\] For example, most athletes with OTS exhibit only a few SAS, and some athletes report no symptoms whatsoever.\[9\] Second, OTS presents different SAS in cases of acute versus chronic performance decrements (e.g. over-reaching vs overtraining).\[4\] Third, excessive training volume may affect the body differently from excessive training intensity; these components may also result in a different constellation of SAS.\[6\] Fourth, two theoretical types of OTS have been proposed. In each, a different part of the autonomic nervous system supposedly predominates: sympathetic or parasympathetic.\[4,19\] This distinction originated from the observations of European sports medicine physicians, circa 1976, who observed that overtraining in different sports elicited different manifestations. Because these two branches of the autonomic nervous system usually counteract each other, the SAS of these OTS types may be opposite. For example, the ‘sympathetic’ form of OTS exhibits insomnia, irritability, restlessness as well as increased heart rate and blood pressure; whereas the ‘parasympathetic’ form exhibits fatigue, depression, apathy and low resting heart rate.\[20\] These forms of OTS both involve impaired performance.\[13\] The sympathetic type is rare and supposedly affects individuals in ‘anaerobic sports’ that involve sprinting, jumping and throwing. The parasympathetic type purportedly affects highly trained endurance athletes in ‘aerobic sports’ such as long-distance running, swimming and road cycling.\[4,13\] Although several authorities state that these two types of OTS exist,\[4-6,13,15,19\] the pathophysiological and pathobiochemical features of each type have not been sufficiently clarified.\[4\] This may be because of the fact that OTS is extremely difficult to elicit in a controlled scientific setting, for both endurance\[6\] and resistance training programmes.\[21\]

Recent evidence suggests that: (i) SAS of OTS in endurance athletes differ from the SAS in resistance-trained athletes;\[6,22\] (ii) different resistance-exercise training protocols produce a variety of neuroendocrine responses;\[6,17\] and (iii) high volume overtraining with resistance exercise is similar

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### Table I. Selected signs and symptoms of overtraining syndrome, as described in published review articles

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>References</th>
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<tbody>
<tr>
<td>Decreased physical performance</td>
<td>4,5,13,15,16</td>
</tr>
<tr>
<td>General fatigue, malaise, loss of vigour</td>
<td>4,5,13,15,16</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4,5,13,15</td>
</tr>
<tr>
<td>Change in appetite</td>
<td>4,5,13,15,16</td>
</tr>
<tr>
<td>Irritable, restless, excitable, anxious</td>
<td>4,5,13,15,16</td>
</tr>
<tr>
<td>Loss of bodyweight</td>
<td>4,5,13,15,16</td>
</tr>
<tr>
<td>Loss of motivation</td>
<td>4,5,15,16</td>
</tr>
<tr>
<td>Lack of mental concentration</td>
<td>4,5,15,16</td>
</tr>
<tr>
<td>Feelings of depression</td>
<td>4,5,13,15,16</td>
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to overtraining with highly aerobic activities, both of which deal with excessively large volumes of exercise.\[6,23\] Given these complexities, a coach or physician conceivably may be faced with a very sophisticated evaluation process: to evaluate OTS on the basis of the type, volume and intensity of training, in a sport-specific manner.\[4,19\] Thus, early and unequivocal recognition of OTS is virtually impossible because the only certain sign is a plateau or decrease in performance during competition or training. Table I summarises nine prominent SAS that were delineated in five review articles published between 1988 and 2000. When a coach or physician identifies these SAS in an athlete, OTS may already exist.

3. The Search for a Mechanism

Despite extensive lists of SAS\[17\] (table I), definitive diagnostic criteria and the biochemical/metabolic mechanism underlying OTS are unknown.\[4-7,16,24\] In attempting to understand the cause(s) of OTS, exercise scientists and physicians have approached OTS from the following perspectives: initiating events, biological markers, fatigue, nutrient imbalance, bodily responses to stressors, hormonal perturbations, immune responses and disturbances of mood state. The following paragraphs describe these attempts to discover the mechanism of OTS.

3.1 Initiating Events

One approach to understanding the aetiology of OTS involves identification of initiating events (e.g. triggers). In addition to an increased volume and/or intensity of a training regimen, these factors have been proposed as possible initiating events: monotony of training,\[13,15\] disease or infections,\[5\] caloric restriction and insufficient carbohydrate intake,\[25\] iron deficiency,\[5\] exercise-heat stress,\[26\] personal and emotional problems, and emotional demands of occupation.\[27\] Scientific support, however, is not strong for most of these potential triggers. Furthermore, identifying these possible initiating events has not revealed the mechanism of OTS.

3.2 Biological Markers

Athletes and the field of sports medicine in general, would benefit greatly if a specific, sensitive, simple diagnostic test existed for the diagnosis of OTS. At present, no laboratory test meets these criteria,\[5\] although a few investigations suggest that selected biological markers offer clues to the mechanism of OTS. Table II presents numerous biological and psychological variables that have been measured in over-reached/overtrained athletes. Unfortunately, none of these hypothetical markers for OTS is unequivocal, and several require confirmation because they are based on only one or two studies. The reader also should note that most of the factors in table II apply to athletes who participate in primarily ‘aerobic sports’; these factors may not be appropriate for OTS caused by ‘anaerobic training’.\[19\]

3.3 Fatigue

In endurance sports, OTS is characterised by persistent fatigue and apathy. A few investigators have examined this fatigue, but its nature has not been clarified. It may be: (i) muscular fatigue; (ii) related to depression; or (iii) the result of an illness. Muscular fatigue ultimately involves an inability to generate energy at a rate sufficient to maintain an activity or performance. The specific energy pathways responsible for muscular fatigue depend on the event duration and intensity. It is possible that energy metabolism, secondary to endocrinological changes [e.g. adrenaline (epinephrine) and cortisol], is altered in OTS and thereby affects fatigue. In one study of depression, fatigue was reported in 56% of patients.\[46\] Various illnesses are associated with fatigue, including anaemia, Lyme disease, mononucleosis, hypoglycaemia, hypothyroidism and chronic fatigue syndrome.\[47\] Several case histories have demonstrated that athletic performance deterioration can be traced to a recent upper respiratory tract infection or a subclinical viral infection that runs a protracted time course.\[48\] Whatever the cause of fatigue during OTS, it is evident that more questions exist than definitive answers.
3.4 Nutrition

Training-induced alterations in nutrient metabolism also have been proposed as contributing factors to OTS, especially as they impact fatigue (see previous paragraph). Two nutritional paradigms have received considerable attention. The first, the central fatigue hypothesis, relates the SAS of OTS to similar symptoms that occur when concentrations of the brain neurotransmitter serotonin increase. Brain serotonin levels have been shown to depend largely on plasma free tryptophan (a metabolic precursor of serotonin), which in turn increases when the concentration of plasma free fatty acids increases. Because endurance training increases plasma free fatty acid levels, this theory proposes that brain serotonin levels increase when training is excessive. A similar, alternative explanation recognizes that branched-chain amino acids and tryptophan compete for the same carrier, in the membrane that composes the blood-brain barrier. This hypothesis posits that decreased concentrations of branched-chain amino acids elevate plasma free tryptophan and brain serotonin levels. Both hypotheses suggest that brain serotonin increases to the point that fatigue and possibly other symptoms of OTS occur, but this cannot be verified presently because present instrumentation cannot distinguish between mechanisms that are mediated centrally or peripherally.

The second nutritional paradigm involves the concept that inadequate carbohydrate intake or a caloric deficiency may encourage the development of OTS. This is supported by the fact that consecutive days of long duration running (e.g. 16 km/d for 3 days) result in decreased levels of muscle glycogen, when carbohydrate intake is constant. Low muscle glycogen levels, in turn, are associated with muscular fatigue. Therefore, some physiologists have examined whether consuming sufficient carbohydrate can maintain muscle glycogen levels and prevent OTS. Although low glycogen levels reduced athletes’ tolerance to increased training, both Snyder and Costill et al. concluded that overtraining for 10 to 14 days was caused by factors other than low intramuscular levels of carbohydrate. Although it has been suggested that chronically elevated catecholamines (e.g. adrenaline and noradrenaline (norepinephrine)), as seen in some overtrained athletes, might encourage OTS by stimulating a reduced rate of glycogen resynthesis.

### Table II. Biological and psychological variables that have been proposed as markers of overtraining (OT), overtraining syndrome (OTS), and over-reaching (OR) [see section 1 for distinctions and definitions]. Despite these investigations, no unequivocal, sensitive diagnostic test exists, other than tests of physical performance.

<table>
<thead>
<tr>
<th>Proposed variables</th>
<th>Experimental design</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>↓ resting and maximal HR</td>
<td>OT, OTS</td>
<td>4,18,28,29</td>
</tr>
<tr>
<td>↑ exercisinga HR and VO₂</td>
<td>OR, OTS</td>
<td>5,30</td>
</tr>
<tr>
<td>↓ maximal aerobic power</td>
<td>OTS</td>
<td>4,10,30</td>
</tr>
<tr>
<td>↓ respiratory exchange ratiob</td>
<td>OT, OTS</td>
<td>18</td>
</tr>
<tr>
<td>↑ nerve excitability</td>
<td>OTS</td>
<td>31</td>
</tr>
<tr>
<td>↑ sympathetic nerve response to stress</td>
<td>OTS</td>
<td>32</td>
</tr>
<tr>
<td>Altered psychological mood state</td>
<td>OR</td>
<td>1,33,34</td>
</tr>
<tr>
<td>Impaired anaerobic energy metabolism</td>
<td>OT</td>
<td>30</td>
</tr>
<tr>
<td>↑ basal metabolic rate</td>
<td>OTS</td>
<td>35</td>
</tr>
<tr>
<td>Negative nitrogen balance (catabolic state)</td>
<td>OTS</td>
<td>35</td>
</tr>
<tr>
<td>↑ infection (upper respiratory and other)</td>
<td>OR</td>
<td>5,36,37</td>
</tr>
</tbody>
</table>

**Blood constituents**

<table>
<thead>
<tr>
<th>Proposed variables</th>
<th>Experimental design</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ haematocrit and haemoglobin</td>
<td>OT</td>
<td>30,38</td>
</tr>
<tr>
<td>↓ leucocytes and immunophenotypesc</td>
<td>OT</td>
<td>39,40</td>
</tr>
<tr>
<td>↓ serum iron and ferritin</td>
<td>OT</td>
<td>29,41</td>
</tr>
<tr>
<td>↓ serum electrolyte levels</td>
<td>OTS</td>
<td>2,23</td>
</tr>
<tr>
<td>↓ serum glucose and free fatty acids</td>
<td>OT</td>
<td>29</td>
</tr>
<tr>
<td>↓ plasma lactate concentrationb</td>
<td>OT, OTS</td>
<td>4,13,18,30</td>
</tr>
<tr>
<td>↑ ammonia</td>
<td>OT, OTS</td>
<td>18</td>
</tr>
<tr>
<td>↓ serum testosterone and cortisol</td>
<td>OR</td>
<td>10,25,33,42</td>
</tr>
<tr>
<td>↓ ACTH, growth hormone, prolactin</td>
<td>OTS</td>
<td>43-45</td>
</tr>
<tr>
<td>↓ catecholaminesd</td>
<td>OTS</td>
<td>4,6,10,24,30</td>
</tr>
<tr>
<td>↑ creatine kinase</td>
<td>OTS</td>
<td>24,42</td>
</tr>
</tbody>
</table>

a During a submaximal exercise test.
b During submaximal and maximal exercise.
c CD3, CD4, CD8, CD14, CD16, CD19, CD45, CD45R0 and CD56 were measured.
d Resting and nocturnal concentrations.

ACTH = corticotropin (adrenocorticotropin hormone); HR = heart rate; VO₂ = oxygen consumption; ↓ indicates decreased; ↑ indicates increased.
post-exercise,\cite{15} no evidence of this effect has been observed.

### 3.5 Bodily Responses to Stressors

It is interesting that stressed employees, students taking examinations, and race horses exhibit SAS similar to those observed in athletes with OTS.\cite{9,54} This is consistent with the concept that OTS reflects the attempt of the human body to cope with psychological and non-psychological stress. Several authorities have observed that OTS represents the sum of multiple life stressors, such as physical training, sleep loss, exposure to environmental stresses (e.g. exposure to heat, humidity, cold, high altitude), occupational pressures, change of residence, and interpersonal difficulties.\cite{4,15,19,54} Thus, OTS can be understood partly, within the context of Hans Selye’s classic general adaptation syndrome (GAS).\cite{15} As a result of animal research, Selye\cite{55} proposed that stressors result in either physiological adaptation or maladaptation. The GAS has three stages: alarm, resistance and exhaustion; all of these stages involve hormonal responses that attempt to re-establish equilibrium.

In the former stage, the body recognises and reacts to stressor(s). In the phase of resistance, the body is able to make appropriate physiological adaptations without illness or damage to organs. In terms of training, over-reaching causes a temporary decline in function that is followed by an adaptation that improves function. When the body has been under stress for an extended period of time, the stage of exhaustion may be reached. At this point, the body’s defence systems are overwhelmed, maladaptation occurs, and normal physiological function is lost for an indefinite period of time. Although many of the symptoms of overtraining are similar to the resistance and exhaustion stages of Selye’s GAS, this model does not clarify the exact mechanism of OTS.

### 3.6 Hormonal Perturbations

The endocrine system is activated to counteract threats (e.g. stressors) to the homeostasis of the internal environment of the body. In response to some exercise-environmental stressors, the brain releases a hormone that causes the release of a second hormone, which then causes the release of a third. Such a sequence is known as a hormonal axis. When the body experiences environmental or internal stressors, two hormonal axes are activated: the sympathetic-adrenal medullary axis (SAM) and the hypothalamic-pituitary-adrenocortical (HPA) axis. Figure 2 depicts the SAM and HPA axes. The distinct effects of these two axes complement each other. Their primary hormone products - adrenaline, noradrenaline, and cortisol - all serve to mobilise and redistribute metabolic fuels at different rates and to enhance the responsiveness of the cardiovascular system. These responses prepare athletes for action and exercise. If over-reaching or overtraining stressors cause tissue injury or trauma, cortisol restrains the initial inflammatory and im-

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**Fig. 2.** The two predominant hormonal axes involved in the body’s response to stressors. The sympathetic-adrenal medullary (SAM) axis involves the sympathetic branch of the autonomic nervous system. The hypothalamic-pituitary-adrenocortical (HPA) axis represents releasing factors (e.g. CRH, ACTH), produced by the hypothalamus and pituitary gland, which lead to responses in the adrenal cortex and other peripheral organs/cells. \textit{ACTH} = corticotropin (adrenocorticotropic hormone); \textit{ADR} = adrenaline (epinephrine); \textit{CRH} = corticotropin-releasing hormone; \textit{NA} = noradrenaline (norepinephrine).
mune responses so that they do not lead to permanent damage.\[56\]

Believing that increased training loads can influence the neuroendocrine environment chronically, research teams\[4-6,22,36,43,57\] have attempted to describe the mechanism involved in OTS by observing the hormonal changes that occur during overtraining and over-reaching. Several extensive reviews and specific investigations\[5,6,15,18,43\] have considered the constellation of endocrinologic changes that occur. Interpretation of these changes is difficult because many factors affect blood concentrations: (i) aerobic and resistance training protocols typically stimulate different endocrinologic responses; (ii) hormone concentrations at rest (chronic adaptation) and during exercise (acute response) respond differently to overtraining; (iii) different resistance training protocols (e.g. number of sets, rest intervals, load, type of muscle action, order of exercise) produce distinct neuroendocrine profiles; and (iv) many hormones exhibit 24-hour cyclic variations.\[6\]

3.7 Immune Responses

Few investigations have evaluated the role of the immune system in OTS. These studies focus on three issues: the association between over-reaching/overtraining and an increased incidence of infection\[36,37,58\], monitoring of leukocytes and other immune factors during periods of overtraining,\[19\] and the possibility that disease and infections may increase the risk of OTS.\[5\] Unfortunately, these investigations provide few mechanisms or models of OTS. Mackinnon\[58\] and Nieman\[48\] have reviewed the literature regarding the effects of OTS on immune function. They concluded that overtrained athletes typically are not immune deficient, by clinical standards, but have an increased risk for upper respiratory tract infection during periods of heavy training and the 1 to 2 weeks following prolonged, intense aerobic exercise training. However, it is possible that immune function during overtraining is compromised by small changes in factors that are important to immune defences.\[37\] For example, suppression of immunoglobulin A secretion has been reported during prolonged periods of intensive training among elite Nordic skiers\[49\] and collegiate swimmers.\[47\]

Today, the endocrine, immune, and nervous systems are seen as one large system serving integrated functions.\[59\] This paradigm is a part of the relatively new field of psychoneuroimmunology, which is devoted to the study of behaviour-brain-immune interrelationships. Interactions between the neuroendocrine and immune systems will be expanded in section 5.5.

3.8 Disturbances of Mood State

The physical demands of overtraining are not the only elements in the development of OTS. Authorities hypothesise that a complex set of psychological factors are important in the development of OTS,\[30\] including excessive expectations from a coach or family, competitive stress, personality structure, social environment, relations with family and friends,\[13,60\] monotony in training, personal or emotional problems, and school- or work-related demands.\[5,15\] Therefore, in search of the mechanism underlying OTS, scientists have measured various psychological factors including subjective complaints, emotional symptoms, and subjective ratings of training effort and fatigue.\[60\] An Australian research team reported that ratings of well-being were effective in predicting improvements in performance.\[61\]

The most fruitful measurements have been of mood, evaluated via the profile of mood states test (POMS).\[62\] The POMS yields a global measure of mood plus separate scores for tension, depression, anger, fatigue, confusion and vigour. The most striking examples of changes in mood have originated from the sport psychology laboratory at the University of Wisconsin-Madison. Spanning 10 years, Morgan and colleagues\[11\] observed more than 400 male and female collegiate swimmers. During these experiments, global mood state scores increased in a dose-response manner as the training stimulus increased, during the course of their competitive seasons. POMS scores fell to baseline levels, with a reduction of the training load at the end of each season. A very similar mood disturbance pattern,
Increasing with training volume and intensity, was observed in collegiate swimmers at the University of Toledo, during a 21-week competitive season.[63] Interestingly, relatively rapid mood changes were detected. During a 3-day period of increased training, POMS scores were significantly disturbed in both male and female swimmers.[8] Mood state also has been used to evaluate overtraining in speed skaters, rowers, canoeists, track and field athletes[9] and distance runners.[64] However, these psychological measurements are descriptive and, to date, do not elucidate the biochemical or neurological mechanisms of OTS.

4. OTS and Depression: A Case Report

An elite marathon runner consulted us before the 1984 summer Olympic games, regarding his preparation for the environmental stressors of heat and humidity that could be expected in Los Angeles.[65] Six years later, he encountered a different problem: a prolonged reduction in his competitive and training performance. His experiences illustrate striking correspondence between depression and OTS.

Laboratory tests, under the guidance of an endocrinologist, indicated that his body had maladapted to years of relentless training. The hypothalamus and pituitary gland were suspected as the points of origin for his difficulties; adrenal exhaustion syndrome[15,26] had been diagnosed. Our advice in August, 1990 (unpublished observations) included: (i) an explanation of the brain’s control of metabolic fuel use and fluid-electrolyte balance; (ii) recognition of the multifactorial nature of his total stress (e.g. running over 160 km/wk, strenuous interval training on the track, frequent carbohydrate depletion, large sweat losses, occupational and family responsibilities); and (iii) techniques to reduce the physiologic strain of strenuous training during summer months.

Formerly an American record holder in three events and the dominant distance runner in the world, this athlete experienced an endless series of illnesses and injuries. His decline in performance lasted for more than a decade. At the age of 34 years, he had tried several approaches to resolve his health problems. He described his odyssey in a way that is reminiscent of table I:

I hated running. I hated it with a passion... In retrospect, I now know what was wrong and what caused my problems. I had three episodes of heat stroke (Falmouth Road Race 1977, NCAA Championships 1981, Boston Marathon 1982). That, combined with all the years of hard training at such a high level without ever taking a break, damaged part of my brain... My endocrine system was so screwed up that I had very low hormone levels... For several years, I was on a wild-goose chase to get my hormone levels normal again. I wasn’t competing anymore but still felt awful. I was always so exhausted I’d fall asleep at my desk at work... I didn’t have the energy to do normal things and was always in a bad mood.[66]

Then, in 1992, he met a physician who ran in masters competitions. Interestingly, this doctor had experienced the constellation of symptoms described above, but had reversed his problems with an antidepressant medication. He shared some preliminary results with the runner, which indicated that athletes with chronic fatigue had responded well to fluoxetine. The runner began taking fluoxetine and within 3 days felt much better, felt more vigorous, and had a renewed zest for life.[66] This antidepressant medication also affected his running performance within 3 days, as evidenced by a workout that included six 1-mile interval runs at 4:42 per mile. He was shocked because he had not run a workout like that in 8 years.

In May, 1994 this runner entered and won the 86.7km comrades marathon in South Africa, defeating his nearest competitor by over 4 minutes. He had not entered any major competition since 1984.[67] He subsequently attributed the success of this antidepressant medication to ‘correction of his medical deficiencies’. He felt healthier in all areas of his life. For example, he had experienced diarrhoea every day for 10 years. After taking fluoxetine, this condition vanished completely.[66]

Other distance runners also may have been assisted by antidepressant medication. This was reported as a part of observations of 30 individuals...
who were undergoing training for a long distance contest. Those who received small doses of an antidepressant (i.e., a monoamine oxidase inhibitor) for 1 to 2 months did not exhibit adrenal exhaustion syndrome or training staleness for at least 1 year. Although performance data were not provided, this report generated a testable hypothesis for future studies.

5. Depression and OTS: Shared Characteristics

The American Psychiatric Association recognizes two subtypes of the condition traditionally named ‘depression’. These include major depressive disorder (MD; known here as major depression) and dysthymic disorder. Major depression affects an individual’s thoughts, feelings, physical health, behaviours, and ability to function in everyday activities. Both biological and psychological components are involved; this medical disorder also may be related to a recent, notable life event such as the loss of a loved one. Although dysthymia lasts for a longer period of time and generally demonstrates less severe symptoms than MD, it may cause impairment in social or occupational functioning.

Major depression involves at least 2 weeks of depressed mood or loss of interest/pleasure in nearly all activities. The individual must experience at least four additional symptoms, as shown in table III. The reader is encouraged to compare these with the SAS of OTS in table I. As noted in the introduction above, this review originated when we recognised that the SAS of OTS were very similar to those of MD. Subsequently, after reviewing previous publications we recognised that OTS and MD share common brain structures, endocrine pathways, and immune responses. We now propose that OTS and MD share a common, or very similar, mechanism (see section 6).

The findings of one research group indicated that a third mood disorder, minor depression, can be identified by utilising the same SAS that clinicians use to diagnose MD (table III). Their face-to-face interviews of 8098 Americans indicated that minor depression occurs in 10% of all citizens, at some point during the lifespan, whereas MD has a lifetime prevalence of 16 to 17%. Minor depression was acknowledged by the American Psychiatric Association in 1994 as worthy of future study.

Nonathletic patients with chronic fatigue commonly exhibit depression and other psychiatric disorders. Among competitive athletes, the most common medical syndrome is that of combined chronic fatigue and depression. In one investigation, Morgan and colleagues reported that up to 80% of athletes with OTS had significantly elevated levels of psychological depression. In fact, experts frequently acknowledge depressed mood or depression as a symptom of OTS.

Two noteworthy reviews provide a theoretical connection between OTS and depression. Both independently hypothesised that highly motivated athletes, consumed with the will to perform well and win, become frustrated by poor performance that may be caused by inadequate recovery during over-reaching and overtraining. Part of this disappointment stems from the athletes’ realisation that they are not living up to pre-established aspirations or goals, despite having invested much in their training programme. Frustration next leads to increased practice time each day and increased training intensity, which results in less regeneration, increased fatigue, and worsening of performance. This progressive cycle of decline also results in deteriora-

Table III. Signs and symptoms of major depression (see section 5 for diagnostic criteria)
tion of an athlete’s mental well-being. Depression then may manifest itself as altered mood states, sleep disturbances, and a loss of zeal for training and competition. Consistent with this theory, Zautra and Reich reported that negative life events (e.g., declining performance) are much more powerful predictors of mental health outcomes than positive events. This suggests that life change per se is not the central dimension that links stressful life events to mood disorders, and that the negative psychological impact of declining performance is an important factor in the development of mood disturbances in OTS. Inconsistent with this theory, the link between depression, negative affect and OTS has been empirically substantiated but without evidence that aspirations or frustration are involved. Thus, this theoretical series of events requires confirmation in future investigations.

It is relevant that the disturbed mood states in both OTS (tables I and II) and MD arise because a complex set of psychological factors exists. Although no authorities doubt that overtraining is the primary cause of OTS, other factors may contribute. Some have proposed that these include excessive expectations from a coach or family, competitive stress, personality structure, social environment, relations with family and friends, monotony in training, personal or emotional problems, and school- or work-related demands. Some have proposed that an individual’s total life stress, the chronic nature of that stress, and the body’s capacity to cope with stress, determine whether OTS, minor depression, or MD occur. Although these concepts require experimental verification, there is consistent evidence for a dose-response relationship between stressful events and depression, and between stressful events and OTS.

Unfortunately, few studies have focused on the biochemical, metabolic and neuroendocrine roles of the brain in OTS, primarily because central nervous system function is extremely complex and it is difficult to measure brain responses with current technology. Although the role of neurotransmitters and receptors in OTS is not well understood, we believe that an examination of the neuroendocrine and immune responses that exist during depression may offer insights into the mechanism and treatment of OTS. The following five sections summarise relevant MD research findings.

5.1 The Role of Neurotransmitters in Major Depressive Disorder (MD) and OTS

No one knows the exact means by which neurotransmitters, neuromodulators and receptors contribute to or are affected by OTS. However, numerous research studies have focused on the roles of serotonin and noradrenaline in MD. We believe that this evidence offers valuable insights into the nature of OTS.

Serotonin is a versatile neurotransmitter that is capable of inducing numerous neurovascular, metabolic and hormonal effects throughout the body. The brain serotonin system is the largest brain system known and has been characterised as a ‘giant’ neuronal system. Brain levels of serotonin are instrumental in the regulation of mood states, sleep, appetite, cognitive function, learning, memory, circadian rhythms, neuroendocrine responses, aggression, sexual activity and motor function. In addition to MD, serotonin has been implicated in schizophrenia, anorexia, bulimia and Alzheimer’s disease.

Several effects of serotonin are important in the aetiology of both MD and OTS (tables I and III), and are indicative of changes in the regulatory and coordinative functions of the hypothalamus. Central serotonergic systems are known to act upon the sympathetic nervous system and the HPA axis (figure 2). Depressed patients exhibit dysfunction of the HPA axis (see section 5.2), as do athletes who exhibit OTS. Furthermore, serotonin influences the regulation of corticotropin (adrenocorticotropic hormone; ACTH), prolactin, growth hormone (GH) and luteinising hormone. Each of these is involved in the body’s responses to stressors (see section 3.6) and hypothalamic function.

Decreased brain serotonin concentrations can precipitate depression in recovered patients with
MD. This reduced brain serotonin may involve abnormalities in tryptophan metabolism.\[77\] Treatments that alter plasma tryptophan and large neutral amino acid concentrations in plasma can positively affect mood in patients with MD. Regarding athletes, tryptophan is a precursor of serotonin that has been hypothetically implicated in acute central fatigue during exercise (see section 3.4).\[48,49\] In one experiment, consumption of an amino acid mixture designed to optimise the tryptophan levels in blood, reduced both physical and mental fatigue in marathon runners, cross country runners and soccer players.\[83-85\] Some authorities have proposed that tryptophan levels, and the consequent serotonin concentrations in brain tissue, play a role in the aetiology of OTS.\[28,49\] Future research may find similar roles for other neurotransmitter precursors such as tyrosine, the precursor for the catecholamines (e.g. noradrenaline, adrenaline, dopamine) and choline which is the precursor for acetylcholine.\[86,87\]

There is extensive evidence that serotonin plays an important role in making individuals vulnerable to an episode of depression, in the precipitation of an episode of MD, and in the action of antidepressant drugs.\[77\] Specifically, the loss of serotonin in the mature brain could compromise the adaptability and stability of neural tissue to dynamically and effectively respond to stimuli from the external environment.\[88\] This may occur because serotonin interacts with other neurochemicals. These other neurotransmitters and modulators, especially noradrenaline and dopamine,\[77\] can initiate opposite actions on the same function, compete for similar target areas in the brain, and share complimentary anatomical distributions in the hypothalamus.\[76\] The reader is reminded that at least seven neurochemicals integrate the body’s responses to stressors: noradrenaline, adrenaline, serotonin, dopamine, γ-aminobutyric acid (GABA), endogenous opioids and acetylcholine.\[59\] As a germane clinical example, abundant evidence indicates that serotonin,\[89\] noradrenaline,\[90\] GABA, endogenous opioids and dopamine\[91\] neurons are implicated in MD and other mood disorders;\[79,92,93\] interactions of serotonin receptor subtypes (see section 5.3) also play a role in MD.\[77\] Similarly, numerous studies suggest that multiple neurotransmitters are involved in OTS.\[75\]

5.2 Neuroendocrine Responses in MD and OTS

The interactions of serotonin, noradrenaline, dopamine and other neurotransmitters directly or indirectly influence many central and peripheral physiologic responses, via the endocrine system. Indeed, the scientific and clinical literature indicates that MD involves abnormal neuroendocrine regulation of the body’s responses to stressors. Patients with depression, for example, exhibit dysfunction of the HPA axis\[78,92,94\] (figure 2), through decreased circulating cortisol levels.\[92\]

Observations of patients with depression in two studies,\[77,79\] at rest and during exercise, indicated that a state of hyperparasympathetic activity exists in MD. This conclusion was made by evaluating blood platelet serotonin concentrations. Utilising a comparison of symptoms among many sports, athletes who overtrain mostly via aerobic exercise (e.g. endurance athletes) exhibit OTS that has been classified as ‘parasympathetic’\[4-6,13,15,19\] (see section 2). The SAS of OTS in table I represent characteristics that predominantly reflect this parasympathetic type of overtraining – the most common variety of OTS. A comparison of the SAS of sympathetic OTS and parasympathetic OTS appears in section 2.

In OTS, hormonal evidence typically appears in blood as a decreased cortisol level at rest (e.g. chronic adaptation) and with exercise (e.g. acute response)\[10,60,64,95,96\] in endurance athletes (table IV), but as an increased, decreased or unchanged cortisol level in anaerobic or resistance-trained athletes;\[6\] decreased testosterone concentration (e.g. chronic adaptation);\[5,6,15,63,95,97\] decreased GH level;\[4,43,60\] and decreased prolactin concentration.\[4,15,55\] The levels of noradrenaline and adrenaline in blood depend on the duration and intensity of the stress.\[6,10,24,60,61,95\]

However, cortisol (e.g. HPA axis) and catecholamine (e.g. SAM axis) concentrations change as
over-reaching advances to overtraining, and as organs adapt to lengthy periods of increased training volume/intensity.\cite{6,57,98} As an example, table IV depicts our interpretation of the likely course of cortisol changes that occurs in endurance athletes, when they transition from acute overload to OTS (figure 1); this table represents a composite of 10 investigations. The work of Beyer and colleagues\cite{99} is included here because they measured the plasma hormone concentrations of 22 experienced middle-distance runners, as their training volume increased from 105 to 120% in 2 weeks. Verde et al.\cite{64} observed a very similar pattern of cortisol levels in highly trained distance runners, by the third week of overtraining (38% increment). Table IV illustrates the dynamic nature of these responses and explains, in part, why physiologists disagree on the course of cortisol changes throughout a competitive season.\cite{6,57,60,98,100} Table IV also demonstrates why the testosterone-to-cortisol concentration ratio (T/C) is difficult to interpret and is considered to be only a gross indirect measure of anabolic-catabolic status;\cite{6,57,60} it is possible that both hormones change as OTS develops. However, circulating testosterone concentrations per se may be useful as a biological marker of OTS, as described below.

Overtrained athletes experience HPA axis dysfunction,\cite{13,43,57,60,75,80} with possible adrenal insufficiency.\cite{15,23,61,101} This latter condition results from overwhelming chronic environmental or physical stress (e.g. overtraining) and ultimately results in reduced circulating cortisol (table II);\cite{10,60,64,95,96} ACTH, GH and prolactin.\cite{43} Research conducted from 1964 to 1977 offers insights into such cortisol reductions. Sulman and colleagues\cite{26} examined human responses to extremely hot, dry weather fronts that included intense desert winds. Known as the Sharav, this meteorological phenomenon is notorious for causing depression, apathy and fatigue in some individuals. Other individuals experience contradictory complaints. To differentiate these individuals, urine samples of 200 patients were analysed\cite{102} for noradrenaline, adrenaline, the cortisol metabolite 17-OH, serotonin, thyroxine and histamine. Analyses indicated that 44% of the people exposed to the Sharav winds had depletion of adrenaline, noradrenaline (both produced in the adrenal medulla) and adrenal corticosteroids (produced in the adrenal cortex). They were diagnosed with adrenal exhaustion syndrome. Their symptoms reflected catecholamine deficiency: fatigue, exhaustion, apathy, depression, lack of concentration and confusion. A second group of patients, those with serotonin irritation syndrome, comprised 43% of the total sample. Their symptoms included sleeplessness, irritability, tension, migraine headaches and a host of other complaints. The third group (13% of the sample), diagnosed with intermittent hyperthyroidism, presented with a mixture of clinical complaints. A retrospective look at the data is interesting for two reasons. First, both the SAM and HPA hormonal axes were disturbed by this severe climatic stress. Second, the symptoms of adrenal exhaustion syndrome were similar to those of the ‘parasympathetic’ form of OTS, whereas the symptoms of the serotonin irritation syndrome resembled the symptoms of the ‘sympathetic’ type of OTS\cite{20} (see sections 2 and 6.1). Adrenal medullary exhaustion altered the ratio of parasympathetic-sympathetic tone in Sharav-sensitive patients, resulting in their unique symptomatology. Reduced adrenal medullary activity may also explain why a cardiovascular autonomic imbalance has been reported in overtrained endurance athletes;\cite{103} power spectral analysis of their heart rate variability indicates a predominance of parasympathetic tone. Therefore, the observa-
tions of Sulman et al.\textsuperscript{[26]} provide a model for future evaluation of the mechanisms of different forms of OTS.

Serum cortisol (a product of the HPA axis) may desensitise higher brain centres.\textsuperscript{[74]} For example, the hypothalamus, pituitary, and hippocampus normally inhibit secretions of the HPA axis during stressful situations, in response to acute negative feedback provided by elevated circulating cortisol.\textsuperscript{[78]} This response is minimised when cortisol levels are chronically elevated (e.g. some forms of OTS), because the function\textsuperscript{[104]} and number\textsuperscript{[74]} of neurotransmitter receptors is altered, or the release of neurotransmitter is reduced, resulting in the loss of normal HPA axis inhibition. In fact, the OTS studies of Barron et al.,\textsuperscript{[43]} Adlercreutz et al.\textsuperscript{[105]} and Lehmann et al.\textsuperscript{[106]} suggest that this dysfunction originates in either the hypothalamus or pituitary. Our recommendations (section 8.1) incorporate this fact.

5.3 Receptors in MD and OTS

Neurotransmitters in neurons and hormones in target organs are recognised at the surface of cells by integral proteins that span the width of cell membranes. Receptor number can be increased (e.g. up-regulated) or decreased (down-regulated) by transcription and translation of the genetic code of the cell, and by destruction of receptors during the course of their function.\textsuperscript{[107]} In this way, the responsiveness of neurons or target tissues changes, as the number of active receptors changes. Depending on the nature of the insult, chronic exposure to stressors may lead to altered receptor responsiveness in the form of unchanged, increased or decreased receptor function.\textsuperscript{[75]}

At least five distinct serotonin receptors have been identified in cell membranes, each with a unique molecular structure, pharmacologic action, and anatomical distribution in the central nervous system.\textsuperscript{[76]} These receptors play a role in both OTS and MD. For example, the serotonin 5-HT\textsubscript{2} receptors in animals are known to adapt to both exercise training and antidepressant medications.\textsuperscript{[108]} Consistent with this finding, research indicates that changes in the sensitivity, or down-regulation, of central and peripheral serotonin receptors\textsuperscript{[78]} may play an acute role in fatigue during prolonged exercise\textsuperscript{[82]} and in the adaptation of the body to chronic endurance training.\textsuperscript{[109]}

Changes in receptor number may persist, despite changes in the release of hormones at the hypothalamic or pituitary gland. For example, the adrenal exhaustion syndrome described in section 5.2\textsuperscript{[26,102]} likely results from changes in the number of receptors in neurons or target tissues; this was not appreciated previously, because receptor function was not as well understood 30 to 40 years ago. Similarly, patients with depression demonstrate changes in receptor function. The theories of MD involving serotonin and noradrenaline focus on changes in the number/activity of membrane receptors, on both sides of the synaptic junction between brain neurons.\textsuperscript{[90,110]} For example, the density of serotonin 5-HT\textsubscript{2} receptors in the brains of patients with MD who committed suicide was different from controls;\textsuperscript{[77,111]} this change in receptor number can be reversed by treatment with antidepressant medication.\textsuperscript{[110]} Interestingly, it is likely that both serotonin and noradrenaline receptors are down-regulated in MD, and that these neurotransmitter systems interact.\textsuperscript{[93]} This may be associated with dysregulation of both the HPA and SAM axes that has been observed in patients with MD.\textsuperscript{[94]}

The existence of receptor down-regulation does not exclude the possibility that other neuroendocrine abnormalities exist. Reports of reduced levels of circulating GH, luteinising hormone, β-endorphin and thyroid-stimulating hormone in overtrained athletes\textsuperscript{[57]} may involve not only reduced receptor numbers, but also decreased production of these biochemicals by the brain. Reviews by Keizer\textsuperscript{[57]} and Meeusen\textsuperscript{[74]} emphasise that both mechanisms may occur in OTS. The same may be true for MD.

5.4 Synaptic Plasticity in MD and OTS

Historically, neuroscientists believed that the adult brain contains static neural pathways, established during childhood development. Research has shown, however, that the adult brain has a remarkable capacity to modify responses throughout life,
including immediate functional modifications and long-lasting structural alterations. The term neural plasticity refers to such alterations and is defined as the process whereby patterns of impulses into mature synapses can cause long-lasting changes in the magnitude of the subsequent stimulation.

Chronic changes in synapse morphology have been induced by repetition of activities, in various species, in different brain areas, and in response to the presentation of distinct stimuli. Animal research has shown that repetitive nerve activation may be expressed as increased synaptic number, thickness, curvature, or complexity via activation of gene expression and new protein synthesis. Such chronic changes in neuron morphology have been observed following the use of divergent experimental protocols such as environmental enrichment, changes of hydration status, behavioural training, neural stimulation and imprinting. Unfortunately, some changes in neurons are detrimental to human health and performance. These involve a decrease in synaptic efficiency and/or a measurable reduction in the size of axon or dendrite dimensions. Down's syndrome, Alzheimer's disease, mental retardation, schizophrenia and some forms of forgetting all reportedly involve decreases in the number of functional synapses.

It is reasonable to hypothesise that OTS involves alterations in neuronal number, thickness, curvature, or complexity because studies have shown that neural plasticity is one form of adaptation to exercise and chronic physical training. A Japanese team examined the effects of running on brain nerve terminals in 1991. When rats received a prolonged, severe running stress, neurons retracted or degenerated in the cerebral cortex (e.g. locus coeruleus). In contrast, mild stress enhanced the sprouting of neurons in this brain area. Thus, neural plasticity may increase or decrease the number of synaptic connections, depending on the degree of stress encountered. In our laboratory, Deschenes et al. observed that different types of exercise (e.g. endurance vs resistance training) resulted in differences in the shape and area of neuromuscular junction synapses in rat skeletal muscle. Further, the testosterone receptor content of muscle, after endurance and resistance training, was different in fast-twitch versus slow-twitch fibres. Our research team proposed that differences in testosterone availability may have stimulated these fibre type-specific changes in testosterone receptor content. Although the role of neural plasticity in OTS has not been examined specifically in humans, it is feasible that our observations could explain the different types of OTS, as well as the divergent SAS, that exist in aerobic and anaerobic sports.

Animal experiments also have been used to explore neural plasticity in simulations of clinical depression. Two unique stressful protocols resulted in retraction or degeneration of brain noradrenaline neurons. Antidepressant medications reversed this response, as evidenced by regeneration of brain noradrenaline neurons. Furthermore, changes in noradrenaline receptors have also been observed after administration of two antidepressant medications. Although the relevance of an animal model to human MD can be questioned, a recent investigation of humans with manic depression indicated that 1 month of lithium treatment increased the volume of grey matter in the brain. A similar study hinted that lithium stimulates production of new brain cells. These findings are the first demonstration of a pharmacological increase of human brain matter, and they support a radical new theory that the birth and death of brain cells underlie the pathophysiology of depression. Given the similarities that MD and OTS share, it is possible that neural plasticity is involved in the aetiology of OTS.

5.5 Immune System Activation in MD and OTS

Figure 2 depicts the SAM and HPA hormonal axes, which provide the body's primary responses to stress. Adrenaline, noradrenaline, and cortisol prepare athletes for action and exercise. If over-reaching or overtraining stressors cause tissue injury or trauma, cortisol restrains the initial inflam-
matory and immune responses so that they do not lead to permanent damage. This interaction between the endocrine and the immune systems is only one of many that are known.

Figure 3 illustrates brain-immune system interactions. The rectangle in the lower right corner represents a group of chemical messengers, the cytokines, that are released into the blood in response to tissue injury, infection, and the chemical by-products of stress. These messengers are critical to survival and include the biochemicals interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-α (TNFα). Cytokines are produced by a variety of cells, including immune, endothelial and fat-storing cells. They act in a way that resembles a diffuse sensory organ, in that they provide the central nervous system with information about a variety of processes occurring in the periphery of the body. The most commonly described action of cytokines is their release from immune cells and, like cortisol, their mediation of inflammation via feedback to the brain.

The increases in circulating cytokines following infection are similar to the changes produced by psychological stressors. For example, immune system activation stimulates the same regions of the brain and releases the same neurotransmitters (e.g. serotonin and noradrenaline) that stressors stimulate. These facts may explain why researchers who study infection and immune activation: (i) often describe the behavioural state observed during sickness in animals as a depressed mood; (ii) acknowledge depression as the most consistently reported symptom of infectious disease in humans; (iii) report depressed mood in humans who receive injections of cytokines; and (iv) observe that peripheral infections change brain serotonin levels markedly.

Consistent with these findings, numerous studies have shown that MD and severe life events, such as the death of a spouse, are accompanied by immune activation throughout the entire body. Furthermore, the HPA axis dysfunction and hormonal changes that occur with MD resemble those that occur during an immune response. Indeed, a theoretical regulatory circuit may exist between the immune apparatus, the HPA axis, and β-endorphin. However, these interactions do not mean that depression is caused by immune system activation. Rather, the prevalent theory states that psychological stress stimulates cytokine release, which in turn maintains depression. One Belgian research team has proposed that multiple, complex interactions occur between brain serotonin levels, immune activation and MD. These interactions are marked in patients with MD by decreased plasma tryptophan levels (as they are in OTS, see section 3.4); tryptophan is a metabolic precursor of serotonin. Other investigators note that the neurotransmitters serotonin and noradrenaline are involved in both MD and immune activation.

Because several case histories demonstrate that diminished athletic performance can be traced to a recent upper respiratory tract or viral infection, numerous studies have considered the role of...
immune system in overtrained athletes. One examined distance runners after the 1997 Copenhagen marathon. This strenuous exercise (2.7 to 4.3 hour duration) induced an increase in inflammatory cytokines (IL-1, IL-6, TNF-α). During 4 hours post-race, an increase in anti-inflammatory cytokines and cytokine inhibitors occurred, which restricted the magnitude and duration of the inflammatory response. Based on such findings, a recent theory of OTS emphasises the role of cytokines in over-reaching and overtraining. The variety of cytokines (e.g. interferons, interleukins, TNFα growth factors, chemokines) provides an explanation for the variety of individual responses and vast numbers of SAS observed in OTS. However, as with MD (see previous paragraph), it is more likely that cytokine messengers maintain, rather than cause, OTS.

In summary, OTS and MD share a large number of characteristics, as shown in table V. Our interpretation of the scientific and clinical literature indicates that the following characteristics of OTS also exist:

- testosteron levels decrease in blood (e.g. chronic adaptation)
- noradrenaline and adrenaline changes in blood depend on the duration and intensity of the stress
- blood GH decreases
- blood prolactin decreases

No research has evaluated these variables in MD, to our knowledge. Therefore, as a test of our

### Table V. Characteristics that are common to both overtraining syndrome (OTS) and major depression (MD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Supporting references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerous factors initiate this disorder</td>
<td>5,13,15,25,26,28,32,51,75,96</td>
</tr>
<tr>
<td>Selye’s general adaptation syndrome model is relevant to the aetiology of this disorder</td>
<td>6,15,75,78,79,92,94</td>
</tr>
<tr>
<td>Increased training load (OTS) or stress (MD) increases the SAS in a dose-response manner</td>
<td>1,17</td>
</tr>
<tr>
<td>Mental and physical performance are greatly impaired</td>
<td>1,5,13,15,30,60,64,95</td>
</tr>
<tr>
<td>Mood changes occur</td>
<td>1,5,13,15,30,60</td>
</tr>
<tr>
<td>Resolution requires weeks or months of rest (OTS and MD) or active rest (OTS)</td>
<td>12,15,68,69,96</td>
</tr>
<tr>
<td>The clinical features vary among individuals (OTS and MD) and among training regimens (OTS); SAS are nonspecific and numerous (OTS and MD)</td>
<td>3,4,6,10,11,17,22,23</td>
</tr>
<tr>
<td>Autonomic nervous system balance (e.g. sympathetic vs parasympathetic tone) is altered</td>
<td>4-6,13,15,19,75,78,92,94</td>
</tr>
<tr>
<td>Brain and neuroendocrine dysfunctions exist; both the SAM and HPA axes are disrupted</td>
<td>10,15,32,43,57,60,75,80,95,96</td>
</tr>
<tr>
<td>The SAS are indicative of changes in hypothalamic regulation</td>
<td>57,98 table I, figure 2</td>
</tr>
<tr>
<td>Serum cortisol levels eventually decrease with exercise (e.g. acute response)</td>
<td>6,10,60,64,95,78,92,94</td>
</tr>
<tr>
<td>in endurance athletes (OTS); resting serum cortisol levels eventually decrease (e.g. chronic adaptation; OTS and MD)</td>
<td>4-6,13,15,19,75</td>
</tr>
<tr>
<td>Adrenal dysfunction may occur in OTS and occurs in MD</td>
<td>15,23,61,96,101,106,78,92,94</td>
</tr>
<tr>
<td>Immune system activation parallels the development of this disorder</td>
<td>17,11,16,17,136,78,92,94,133,134</td>
</tr>
<tr>
<td>Neurotransmitter release and/or membrane receptor sensitivity may change as this disorder develops</td>
<td>23,54,57,61,75,101,109,78,92,94</td>
</tr>
<tr>
<td>Neural plasticity has been implicated</td>
<td>112,120-123,120,124-128,78,92,94</td>
</tr>
<tr>
<td>Multiple neurotransmitters are involved</td>
<td>75,78,92,94</td>
</tr>
<tr>
<td>Brain serotonin concentration may be related to fatigue (OTS); is an aetiological factor (MD)</td>
<td>28,49,50,76,78,91,108,136</td>
</tr>
<tr>
<td>Cytokine messengers play a role in this disorder</td>
<td>16,78,131,133,135</td>
</tr>
</tbody>
</table>

HPA = hypothalamic-pituitary-adrenocortical axis; SAM = sympathetic-adrenal medullary axis; SAS = signs and symptoms.
theory that OTS and MD have similar aetiological mechanisms, we hypothesise that future research will confirm these responses in patients with MD.

6. A Novel Perspective on OTS

We believe that the mechanisms of the various types of OTS are distinct and can be understood best when three factors are considered. First, athletes with OTS experience either HPA axis dysfunction with possible adrenal insufficiency, SAM axis dysfunction, or both. Second, OTS dysfunctions likely originate in either the hypothalamus or pituitary. Third, interactions of different neurotransmitter systems (e.g. serotonergic, noradrenergic) are likely involved in OTS.

6.1 Autonomic Balance and the Sympathetic-Adrenal Medullary Axis

Different training regimens result in OTS varieties that are difficult to distinguish. To illustrate this fact, table VI presents an analysis of the sympathetic and parasympathetic aspects of the autonomic nervous system in several athletic and nonathletic populations. The basal rate of sympathetic and parasympathetic activity is known as tone. A balance of sympathetic and parasympathetic tone is required for numerous vital functions, including blood vessel constriction/dilation, heart rate, and gastrointestinal motility. Most of the body’s sympathetic activity originates from basal secretions of noradrenaline and adrenaline in the adrenal medulla. Thus, column 3 in table VI represents activity of the SAM axis. Increased sympathetic tone is chronically experienced by athletes who overtrain via intense, anaerobic training methods [see ‘athletes with anaerobic form of OTS (AN-OTS)’ and ‘resistance exercise, increased training intensity (R-ITI)’]. In contrast, parasympathetic tone predominates in athletes who increase training volume greatly [see ‘athletes with aerobic form of OTS (A-OTS)’ and ‘resistance exercise, increased training volume (R-ITV)’].

6.2 Cortisol and the Hypothalamic-Pituitary-Adrenocortical Axis

Table VI also compares circulating cortisol levels and HPA axis function (column 2) in athletes and nonathletes. Of particular interest are the four varieties of overtraining. Athletes who encounter intense exercise overload (e.g. AN-OTS and R-ITI) show a variety of cortisol responses, depending on the specific stressors encountered and the point at which observations are made. In contrast, athletes who experience a training volume overload (e.g. A-OTS and R-ITV) exhibit either increased or decreased cortisol levels, depending on the type of the exercise.

Combined, columns 2 and 3 of table VI represent the function of both the HPA axis (e.g. circulating cortisol concentration) and SAM axis (e.g. sympathetic-parasympathetic balance). We propose

<table>
<thead>
<tr>
<th>Participants</th>
<th>Chronic blood cortisol response</th>
<th>Chronic sympathetic nervous system effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults</td>
<td>↔</td>
<td>=</td>
<td>92</td>
</tr>
<tr>
<td>DD patients</td>
<td>↔</td>
<td>↓</td>
<td>92</td>
</tr>
<tr>
<td>MD patients</td>
<td>↓</td>
<td>↓</td>
<td>92</td>
</tr>
<tr>
<td>A-OTS patients</td>
<td>↓</td>
<td>↓</td>
<td>5,10,43,60,64,95,96,103</td>
</tr>
<tr>
<td>AN-OTS athletes</td>
<td>↑↓↔</td>
<td>↑</td>
<td>6</td>
</tr>
<tr>
<td>R-ITI athletes</td>
<td>↓↔</td>
<td>↑</td>
<td>6</td>
</tr>
<tr>
<td>R-ITV athletes</td>
<td>↑</td>
<td>↓</td>
<td>6</td>
</tr>
</tbody>
</table>

AN-OTS = athletes with anaerobic form of OTS; A-OTS = athletes with aerobic form of OTS; DD = patients with dysthymic disorder; MD = patients with major depression; R-ITI = resistance exercise, increased training intensity; R-ITV = resistance exercise, increased training volume; ↓ indicates decrease; ↑ indicates increase; ↔ indicates no change; = indicates balanced sympathetic-parasympathetic tone.
that this perspective of neuroendocrine function offers a method to test potential treatments for OTS in various athletic events.

7. Potential Pharmacologic Therapies for OTS

Just as the outcome of MD drug therapies are not certain, and the dose and type of medication used in mood disorders may be revised after observing patient responses, there presently is no definitive treatment for OTS. Furthermore, we believe that drug treatments for OTS will someday be based on the relative proportion of serotonin, noradrenaline, and other neurotransmitters required to restore normal balance of brain function.

Other than specific treatment for diagnosed cases of MD among athletes,[72] we have found only a few general recommendations for antidepressants in the treatment of OTS.[1,142] However, because this manuscript presents many striking similarities between OTS and MD, and because it distinguishes various types of overtraining, we believe that a pharmacologic approach to OTS should be considered, may restore performance, and may reduce the SAS (table I). Future studies should at least examine the efficacy of various antidepressant medications in returning overtrained athletes to their former levels of performance and vigour.

Because different types of OTS involve unique neuroendocrine responses (table VI), it is possible that they also may respond to different drug therapies. For example, HPA axis function (column 2 in table VI) is modulated by the serotonin system and SAM axis function (column 3 in table VI) involves the neurotransmitter noradrenaline. If future investigations verify or modify the information in tables IV and V, specific antidepressant medications or other pharmacologic approaches may be utilised to reverse neuroendocrine dysfunction(s) in overtrained athletes.

Knowledge has grown considerably within the past decade regarding the mechanisms by which antidepressants work.[93,110,143] The categories of action include: blockade of neurotransmitter nerve endings (e.g. serotonin, noradrenaline, dopamine), blockade of receptors (e.g. serotonin, histamine, noradrenaline, dopamine), inhibition of monoamine oxidase, or potentiation of serotonin and noradrenaline effects.[93,144] Table VII provides a classification of selected antidepressant medications, mechanisms of action, and generic names of products available in the US. We propose that these antidepressants may someday be matched to specific neurotransmitter deficits (table VII).

7.1 Caveats

Presently, little guidance can be offered to physicians regarding prescription of newer antidepressant types (e.g. selective noradrenaline reuptake inhibitors),[144] and relatively little is known about the effects of antidepressants on children and adolescents.[145] To complicate matters, multiple neurotransmitters may exist within a single sympathetic or parasympathetic neuron.[146] These facts suggest that we have much to learn about the efficacy of antidepressant medications as therapies for OTS.

We also acknowledge that antidepressants may cause enhanced heat storage during exercise-heat exposure. For example, a patient with depression experienced heatstroke after 4 hours of labour in a hot environment. His depression had been treated with a combination of fluoxetine and lithium,[147]
and his hyperthermia may have been associated with these medications. We recommend that antidepressants be tested thoroughly, in controlled exercise trials conducted at various environmental temperatures, before being prescribed for athletes who exercise in hot environments.

8. Considerations for Coaches and Physicians

As research continues, the complexities of OTS (table VI) will be better understood. Until that time, coaches and athletes will continue to rely on performance decrements as verification that OTS exists. However, if sophisticated laboratory techniques (e.g. testosterone assays) are not available, the following considerations may be useful:

8.1 OTS

- Maintain accurate records of performance during training and competition. Be willing to adjust daily training intensity/volume, or allow a day of complete rest, when performance declines. During periods of heavy over-reaching, individualise the intensity of training.
- Encourage and regularly reinforce optimal nutrition, hydration and sleep.
- Be aware that multiple life stressors (e.g. sleep loss, exposure to environmental stressors, occupational pressures, change of residence, and interpersonal or family difficulties) may add to the stress of physical training.
- Treat OTS with rest. Reduced training may be sufficient for recovery in some cases of over-reaching.
- Because total inactivity can be a significant source of stress for competitive athletes, active recreation may aid recovery and may help deter monotony. Resumption of training should be individualised on the basis of SAS (table I) because there is no definitive indicator of recovery. It would be helpful to find ways to make rest more appealing to athletes.
- Encourage athletes to communicate with you about their physical, mental, and emotional concerns.
- Consider questionnaires or interviews to determine changes in mood state. Although several psychological instruments are available, a psychologist should be consulted for guidance. Monitoring of mood states during a given macrocycle offers a potential method of quantifying distress and titrating training loads on an individual basis.

8.2 MD

- Acknowledge that OTS and MD share many characteristics.
- Athletes experience MD and dysthymic disorder. Various reports of MD and other mood disorders among professional athletes have been published in recent years (see case report: section 4). Up to 80% of athletes with OTS have elevated levels of psychological depression.
- Adolescents and young adults often value athletic success highly. Sport plays a critical role in their psychosocial development and can be an important source of self-esteem during a critical, volatile period of self-concept edification. A revealing high school case study described how negative experiences in sport may contribute to feelings of inadequacy, helplessness, hopelessness, and ultimately lead to MD and chronic fatigue. In some athletes, the first experience with OTS, and failure to meet important competitive goals, may be emotionally devastating.
- Maintain confidentiality regarding each athlete’s condition. A diagnosis of MD is fraught with social stigmatisation and often is viewed as a personal failure, a loss of willpower, or a character defect. For these reasons, an athlete often denies the condition.
- The most common medical syndrome among competitive athletes is that of combined chronic fatigue and depression. An athlete that exhibits chronic fatigue or depression may be ill with a condition other than OTS or MD. Figure 4 presents a variety of illnesses that a physician will consider during diagnosis. If other illness are ruled-out, then a training break is necessary.
Do not interfere with athletes who have developed ways of coping with psychological stressors. If minor depression or MD is suspected, athletes should be referred to a psychotherapist. Among all US citizens, MD has a lifetime prevalence of 16 to 17%. Professional crisis intervention ordinarily requires 4 to 6 sessions. The effectiveness of such counselling will depend on the clinician’s prior understanding of each athlete and on establishing a relationship before any need the athlete may have. The sports medicine physician or family practitioner can be very helpful in determining whether psychotherapy is necessary.

9. Conclusion

The OTS and MD share numerous signs, symptoms, brain structures, neurotransmitters, endocrine pathway dysfunctions and immune responses. This suggests that their aetiologies are similar and raises the possibility that medications prescribed for MD (i.e. antidepressants) may effectively treat OTS. However, the varieties of OTS are difficult to distinguish and are not completely understood, perhaps because multiple neurotransmitters are involved, the number of neurotransmitter receptors changes, or neural plasticity (e.g. a decrease or increase in the number of synapses) is involved. Further, little definitive guidance presently can be offered to physicians regarding prescription of newer antidepressant medications. Therefore, we strongly recommend controlled research studies that evaluate the effects of various antidepressant medications on variants of OTS.

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References


82. Azmitia EC. Serotonin neurons, neuromodulation and homeostasis of neural tissue. Neuropsychopharmacology 1999; 21: 335-455
88. Azmitia EC. Serotonin neurons, neurol plasticity, and homeostasis of neural tissue. Neuropsychopharmacology 1999; 21: 335-455
140. Wischnia B. A time to reflect. Runners World 1994; 29 (9): 80-4
150. Wertheim LJ. Desperate for a second chance: battling bipolar disorder, former Jazz center Luther Wright dreams of the NBA. Sports Illus 2000; 92 (1): 38-9
151. Lidstone JE, Amundson ML, Amundson LH. Depression and chronic fatigue in the high school student and athlete. Prim Care 1991; 18: 283-96

Correspondence and offprints: Lawrence E. Armstrong, Human Performance Laboratory, Department of Kinesiology, University of Connecticut, 2095 Hillside Road, Storrs, CT 06269-1110, USA.