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Cortisone – the body's Double agent

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Background to cortisone

Until the late 40s of the last century, the fate of people suffering from rheumatoid arthritis was bleak indeed. Apart from the use of high dose aspirin and physical therapies like massage and sauna, there was little to offer the sufferer. In 1948, however, the extraction from animal adrenal glands of natural cortisone, its chemical synthesis, and its clinical use radically transformed the treatment of this dread disease. At last there appeared to be a well-tolerated treatment which was effective when given both orally and by injection. Cortisone, the major human glucocorticoid, became the standard for a range of both natural and synthetic anti-inflammatory agents. It heralded a boon in the management of not only rheumatoid arthritis, but more than 200 (to date) chronic inflammatory, allergic and auto-immune disorders, Diseases like asthma, psoriasis, eczema and uveitis almost overnight became more amenable to effective treatment; organ transplantations became a distinct possibility; and people with adrenal gland failure could be confidently treated.

Alas, although hailed initially as a miracle drug for the astounding improvements shown in arthritic patients, this turned out to be somewhat premature. The understandable excitement was gradually tempered by the realisation that the clinical effect was temporary, and that cortisone's unexpected adverse reactions were numerous, and often severe.

This review will examine the nature, role and clinical use of cortisone and other glucocorticoids, both from the conventional medical and the Tibb perspective. Also the adverse drug reactions brought about by cortisone, in the light of a strong increase in use, and abuse, of these agents.

What is cortisone?

A key regulator of many activities in the body, especially inflammation and the stress response is cortisone. It is one of several natural substances called steroids which are synthesised from the source substance cholesterol. It is secreted from the outer part, or *cortex,* of the adrenal gland in response to internal metabolic changes and external stress

Cortisone and other glucocorticoids differ from anabolic steroids. These are used (and abused) for their ability to build up muscle mass and strength.

The adrenal glands are truly intriguing structures; small in size, but active in virtually every aspect of our body. These endocrine glands, perching one each on top of our two kidneys, have a truly wide range of important effects on the body's daily activities, influencing sugar metabolism, the body's response to stress, regulating salt and water balance, and affecting reproductive function.

Each adrenal gland is actually a combination of two distinct glands, fused together. The outer cortex secretes corticosteroids, such as cortisone, and the inner medulla, the sympathetic agent, adrenaline. Both of these are deeply involved in the stress response.

The adrenal cortex secretes two types of corticosteroids: those like aldosterone, which acts on the kidneys to regulate water and electrolyte balance. This is one of the *mineralocorticoids*. The others are the *glucocorticoids*, of which cortisone is the main member.

Another function of the adrenal cortex is to provide the chemical building blocks for the production of the sex hormones *estrogens* and *testosterone*.

Hormonal control of cortisone release

The secretion of cortisone and related hormones is governed by the *pituitary gland*, which resides in the lower part of the brain. This 'master gland' releases the signaling or *trophic,* hormone adeno-cortico-trophic hormone (ACTH) into the bloodstream. The pituitary gland itself is influenced by the *hypothalamus,* an adjacent structure which interconnects to several other parts of the brain, some of which are involved in emotions. The hypothalamus secretes the local hormone, *corticotrophin releasing factor (CRF),* which acts on a particular part of the pituitary gland.

This hypothalamus – pituitary – adrenal (HPA) axis as it is called relies on a series of hormonal signals to keep the sympathetic nervous system working. If the brain perceives something as dangerous, the hypothalamus releases CRF, which travels to the pituitary gland, triggering the release of ACTH. This hormone travels to the adrenal glands, prompting them to release cortisone and cortisol (a simple derivative). This helps to maintain the body in a state of high alert. When the threat passes, cortisone levels fall, and the process goes into reverse. This 'negative feedback' mechanism dampens the stress response.

How does cortisone work?

Cortisone acts within our body cells. Once it has passed through the cell membrane along special channels, it joins up with a specific receptor carrier protein, and travels along microtubules towards the cell nucleus, where the body's genetic material, or DNA, is located. The cortisone-receptor combination passes into the nucleus, and attach to a pre-determined section of the DNA. Here it organises the formation of a complex substance, RNA, which is very similar chemically – almost a replica – to the part of DNA it attached to. This is termed 'gene expression'. This RNA in turn moves to a structure called a *ribosome*, which is in effect the cell's protein factory. From the instructions embedded in the RNA, the ribosome makes specific mediator substances, which have anti-inflammatory properties. These migrate from the cell into the general circulation, where they act at the site of inflammation when it arrives.

Cortisone acts on a wide range of DNA sites, and the net result is the synthesis of several (more than 20 to date) anti-inflammatory mediator substances. These include *arachidonic acid*, certain *prostaglandins*, *cytokines* and *interleukins.*

Cortisone also suppresses the production of enzymes such as blood vessel dilating *nitric oxide synthase* and tissue modifying enzymes such as *collagenase.*

Example or cortisone use: ***Lupus erythmatosus***

This is a relatively common inflammatory disorder which affects our connective tissue. This is present in virtually every organ and tissue in the body. Lupus appears as an inflamed, red, scaly and butterfly-shaped rash on the cheeks and nose. The sufferer will most likely go on to develop a form of arthritis, and perhaps increasing damage to his or her kidneys. In serious cases, repeated inflammatory episodes damage the heart, lungs and brain, partly due to the formation of scar tissue, or *fibrosis.* Most sufferers are affected by the discoid form of lupus, which confines itself to the skin only. Until the advent of cortisone and its relatives, the only treatments available were anti-inflammatory drugs like aspirin, and immune suppressants. However, present day treatment revolves around cortisone or (more usually) its synthetic derivatives such as prednisone. These are usually very effective in repressing most symptoms, such as joint pain and stiffness, pleurisy (inflammation of the lung) and fever. The painful swelling of the sufferer's face, with warm and tenderness, respond in a few days therapy with cortisone.

The potential for abuse in this disorder is evident. In view of the cosmetic nature of the disorder, the impulse to use higher doses is present, as is the inclination to take cortisone to prevent further attacks.

The 'fight or flight' response

This is our body's basic, inborn and automatic survival response to threats of our personal wellbeing, as attack or bodily harm. It rapidly prepares us to either stand our ground and fight, or when the threat is perceived to be overwhelming, to flee from it. When we are exposed to excessive stress, either from external sources, or arising from internal fear or worry, a basic physiological reflex is triggered. This reflex is 'hard wired' into our nervous system, especially our brain, and our endocrine system, particularly the adrenal glands. It is part of our genetically determined wisdom of the body, recognised in Tibb as Physis.

When this stress response is activated, messages, either as nerve impulses or small hormones, are issued from the brain, initially from the *amygdala,* then the *hypothalamus,* then the *pituitary gland* which travel to the *adrenal glands*. These in turn are stimulated to release hormones, mainly *adrenaline* (from the inner medulla of the gland), and *cortisone* (from the outer cortex).

These hormones bring about a series of rapid and dramatic changes to the body. The first one is an immediate rise in the breathing rate, followed quickly by a rise in blood pressure and blood sugar is mobilized from the liver. This creates the energy reserve which may be used at short notice. Moreover, blood is diverted from where it is not needed, such as the digestive system and liver, to areas where it is, especially the skeletal muscles in the limbs. The body is thus better equipped for fighting or fleeing.

Not only that, but our pupils dilate, so improving our vision markedly. Our general awareness sharpens, our sense of pain deadens, and our general bodily impulses speed up. More slowly, our immune system, an essential part of Physis, goes into active mobilisation, as it anticipates a real need for tissue repair, whether from fight or flight.

Once the threat has passed, then the cortisone continues to act to replenish the depleted energy stores in the liver. As part of this process, the person's appetite is increased, so the stores of fatty tissue around the body, which have been run down to provide energy during the stressful episode, are rebuilt. This can lead to substantial weight gain.

Tibb and stress

Tibb regards good health as the existence of harmony between the person's temperament, the lifestyle he or she has adopted, and the physical environment. This can arise in the immediate outside, environment: physically threatening situations from, for example, exposure to crime and dangerous driving can bring on acute stress very quickly. It can also arise from within: anxiety over money problems, divorce, job loss, etc., will lead to chronic stress.

Stress is common feature of today's fast-paced, pressured, and chaotic lifestyle. It arises from many sources, both physical and emotional. Tibb considers that uncontrolled or long lasting stress is linked to serious imbalances in the qualities of heat with dryness. This occurs as a reaction to any physical, mental or behavioural factor which is beyond the person's ability to handle. This explains the primary symptoms of increased heart rate, panting and diarrhoea.

We now know these are due to the effects on the dominant, but also sub-dominant person of the stress hormones adrenaline and cortisone. It also explains why people who are temperamentally bilious, who have dryness as a major quality are more susceptible to the negative effects of continued stress.

From the Tibb viewpoint, stress includes anything that causes disharmony in the body, whether it is from an injury, or from emotional trauma, or from physical excess, or from social and occupational pressures. Tibb associates abnormal or long lasting stress with the qualities of heat with dryness. There is a serious imbalance in these qualities, which occurs as a reaction to any physical, mental or behavioural factor which is beyond the person's ability to control. This explains the primary symptoms of panting and increased heart rate and, and secondary symptoms such as diarrhoea. We now know these are due to the effects of the stress hormones adrenaline and cortisone. It also explains why people who are bilious in temperament, especially dominant, but also sub-dominant, who have dryness as a major quality, are more susceptible to the negative effects of continued stress.

To deal with either form of stress the body attempts to restore harmony by bringing *Physis* into operation. Physis calls on and regulates a wide range of mechanisms to restore qualitative balance These include stimulating the secretion of the stress hormones, adrenaline and cortisone, the mobilisation of energy-providing glucose from depot tissues such as the liver, and the conversion of fatty acids into glucose.

Physis, stress and cortisone

From the Tibb perspective, the human body is a robust, infinitely complex and self-regulating organism, with an amazing, powerful and long-lasting capacity to heal itself. In the body, each organ and every tissue serves others, and is in turn served itself. No organ is independent; all work together in a holistic fashion to present a cohesive and harmonious organism. To maintain this harmony, all organs are in close contact with each other, and communicate continuously. This intensive communication is carried out by a large number of hormone, chemical factors, and neurotransmitters – all controlled by the body's inherent wisdom in maintaining homeostasis; known in Tibb as *Physis.*

Cortisone is termed a *stress hormone.* It has a major role in the body's mechanisms for dealing with stress. When we are stressed, our blood sugar level rises, as both cortisone and *adrenaline*, the other main stress hormone, spring into action to provide the energy boost when needed soon. Cortisone helps move glucose from its storage sites in the liver and other tissues into the general circulation. This action provides extra energy for essential structures like the heart, brain and skeletal muscle.

When major disharmony arises in the body due to excessive stress, then the body's previous good health is under serious threat.

Clinical uses for cortisone

Inflammation is the common factor is a wide range of chronic and recurring disorders which at first glance seem completely different, with little in common. They affect different tissues, organ systems, and basic functions.

However, diseases as disparate as asthma, cancer, psoriasis, arthritis, certain eye problems and transplant rejection have one feature in common – they are all connected by having excessive or uncontrolled inflammation as the basis for their pathology.

Cortisone is used clinically in three distinct areas:

- **Replacement therapy for a failing adrenal cortex.**
- **As a drug for a wide range of inflammatory diseases.**
- **To prevent organ rejection after transplantation.**

1. Replacement therapy. If a person's natural level of cortisone is too low because the adrenal cortex glands are not working properly, serious problems will arise. This form of adrenal insufficiency occurs in Addison's disease. This was common in the past in some countries where tuberculosis was prevalent. The person affected will succumb to fatigue, general weakness, a range of digestive disorders, and incapacitating joint and muscle pain. More seriously, it can lead to collapse and even death. This clinical emergency can now be quite

easily remedied by administering cortisone or other corticosteroids, which allows the body to function normally once again.

2. Treatment of inflammatory diseases. Cortisone and related glucocorticoids have been routinely used as part of the long-term management of a very wide range of clinical disorders. They are administered either locally (by application to the skin), or orally as tablets or liquid, parentally by injection into the skin, muscle or other tissues.

Their use falls into two distinct areas:

- In disorders where excessive inflammation is present, and causing unacceptable symptom like pain, swelling and stiffness.
- To suppress the immune response, when there is evidence that the disorder is an auto-immune disease. In these conditions, the immune system mistakenly identifies normal tissue and organs as being alien to the body, and attempts to restore balance by trying to eliminate them.

The main clinical applications for cortisone and related agents are summarized in the table below:

Rheumatic disorders	Inflammation of a joint, tendon, cartilage or bursa – rheumatoid, psoriatic, gouty and osteoarthritis, bursitis, gout
Breathing disorders	Acute or chronic inflammation of the breathing passages – Bronchial asthma, pneumonia, tuberculosis, severe sore throat
Allergic states	Acute asthma attacks, contact dermatitis, serum sickness
Skin diseases	Resolving scars, suppressing eczema, psoriasis, urticaria, drug reactions, fungal infections, hives, sarcoidosis, shingles
Disorders of the digestive system	Ulcerative colitis, Crohn's disease, enteritis, sprue
Endocrine disorders	Thyroiditis, adrenal cortex insufficiency
Disorders of the blood forming system	Anaemia of different origins, purpura
Diseases of the eye	Keratitis, eye ulcers, iritis, uveitis, allergic reactions, shingles
Certain cancers	Certain leukaemias and lymphomas
Immune suppression	Autoimmune diseases, after an organ transplant
Various	Tried in lupus, heart & kidney inflammation, multiple sclerosis flare-ups

3. **Organ transplantation.** When an organ, like a lung or kidney, or tissue, lie bone marrow, is transplanted from one person (the *donor)* to another (the *recipient)*, the recipient's Physis recognises the new tissue as being foreign, and sets up a powerful response to eliminate, or *reject,* the tissues of the alien intruder. It does this by mounting a complex rejection process, involving severe inflammation at both the tissue and the cellular level. Corticosteroids, natural and synthetic versions, are often used to suppress this rejection process, so that the transplanted organ or tissue will be allowed to integrate into the recipient's body. . Cortisone or a similar

corticosteroid is part of a cocktail of drugs, including methotrexate and cyclosporine, which is used aggressively to dampen down the rejection process. If successful, the transplant takes hold in the recipient's body, and begins to function properly. However, maintenance treatment with low doses of cortisone is necessary in order to prevent a flare-up of the rejection episode, possibly for many years.

Adverse effects of cortisone

The more bodily stress, arising from chronic pain or inflammation, the more cortisone is released by the adrenal cortex. Cortisone and its related corticosteroids are powerful pharmacological agents. They have a huge impact on the inflammatory and immune system mechanisms, which are immensely important aspects of Physis. It comes as no surprise, therefore, that they are prone to many serious, often devastating, adverse reactions or side effects.

People who take cortisone for an extended period of time, or at high doses, are prone to one or more of the following side effects:

- **Reduced resistance to pathogens**. People's immune system are weakened, so making them more susceptible to coughs and colds and other infections brought on by certain viruses, to fungal infections like thrush, to the development of cancers, and to general bacterial infections. The cortisone may also mask the signs and symptoms of an infection, making them deceptively trivial.
- **Poor wound healing**. This takes much longer than normal after surgery or trauma, The possibility of opportunistic infections increases.
- **Digestive system upsets.** Ulcers in the oesophagus and stomach are common with long term cortisone usage, as is inflammation of the pancreas. Persistent nausea and abdominal distention may occur.
- **Atherosclerosis.** The arteries may harden, partly because of an increase in blood sugar and fats. A rise in blood pressure will also contribute, due to water and sodium retention.
- **Osteoporosis.** Thinning of the bones, making the hip and spine especially more susceptible to fracture. This can be aggravated by progressive skeletal muscle weakness.
- **Diabetes.** This is due to an increase in circulating blood sugar.
- **Physical appearance.** The face becomes flushed, with swollen cheeks, leading to the typical 'moon face'. An increase in appetite can lead to a rapid and evident increase in body weight. This is aggravated by water retention in the body. Abnormal fat deposits form on certain parts of the body – face, chest, back, and abdomen.
- **The skin.** This becomes thin and very fragile, bruising easily. Stretch marks form on the skin at different sites, and acne or pimples appear. Cataracts may develop.
- **Suppressed growth.** This often appears in children, so they are physically smaller than they should be at a certain age.

- **Mental disorders.** The brain is badly affected by excess cortisone. Excess cortisone kills brain cells over time, especially in the hippocampus, where memories are stored. Excess cortisone damages short-term memory as well.
- **Behaviour problems.** People can become irritable for no real reason, or conversely irrationally euphoric. Temper tantrums and the typical 'steroid rage' may occur. Sudden changes in mood are common, as is depression. Insomnia can become a problem.
- **Others.** Headaches, dizziness, cataracts, glaucoma, are known to occur in long-term cortisone treatment.

Long-term effects of cortisone treatment

Cortisone has a marked inhibitory effect on the HPA pathway, which describes the sequence from the pituitary gland, to the hypothalamus, to the adrenal gland cortex. If this influence becomes abnormal, or lasts for too long, clinically significant adverse effects will develop.

The problems associated with long-term, high dose cortisone usage include:

- **Drug dependency.** Once a pattern of regular use is established, people find it very difficult to discontinue cortisone use. The original target ailment generally relapses, with or without the help of cortisone. However, cortisone abusers usually battle to discontinue, and this usually brings a host of problems of their own.
- **The rebound effect.** Many people using cortisone effectively for a particular condition find that it flares up once it is withdrawn at the end of the recommended treatment. This often results in the patient insisting that the cortisone treatment is resumed, often at a higher dose.
- **Adrenal suppression.** During long-term cortisone treatment the adrenal glands gradually shut down its own synthesis and secretion. If the cortisone being given regularly is discontinued abruptly, then the adrenal cortex is unable to compensate by resuming secretion immediately. This means the person is more exposed to stress, and less protected by natural cortisone secretion. This can be prevented by gradually reducing the daily dose over a few weeks, so allowing natural cortisone secretion from the adrenal cortex to resume as previously normal.

Cortisone abuse

The regular use of cortisone is common in many athletes. It prevents any pain reducing their performance, or interfering with their training. It is particularly valuable for professional cyclists, for example, who find it allows them to go through the pain barrier: to "drive through the pain'. In doing so it helps to improve their athletic performance. It was the preferred drug of choice for serious participants in many endurance sports, to the extent that cortisone or similar steroid injections were regarded as routine, almost normal, even common place. As a result, many professional cyclists and other endurance athletes resorted heavily to cortisone injections in the past, especially at a time when testing was not as draconian as it is now.

Cortisone abuse does, however, carry a real, substantial risk. Over-enthusiastic use can backfire spectacularly, with serious, perhaps severe, and possibly catastrophic consequences. Over time, the artificial stimulation of damaged muscle leads to a progressive weakening of not only the skeletal muscles, but the joints these muscles service. When taken at increasingly higher doses the adverse effects begin to outweigh their real or imagined benefits. To start with, headaches, sudden visual disturbances and physical weakness may appear. An abnormal and alarming rapid heartbeat and difficulty when breathing may develop. These symptoms may be followed by the appearance of blood in the stool, a sign of marked internal bleeding. These reactions often require emergency care.

Abuse of cortisone is often a bigger medical issue than the disease for which it was first prescribed. It is very easy to start using cortisone legitimately, but is often very difficult to discontinue it.

For the patient, the following issues need to be addressed:

- Is the cortisone really necessary for this disorder in this particular patient?
- What is the expected outcome, and how long will it take to reach this?
- What are expected effects of withdrawal from treatment with cortisone?
- How long will these adverse effects last, and how can they be counteracted or minimised?
- After discontinuation, will the disease reappear? Will a relapse occur?

Summary

Stress is a natural and constant part our daily lives, and has been since the dawn of human history. The reaction to stress is the so-called “fight or flight” syndrome – the stress, of whatever form it takes, is either opposed by direct confrontation, or avoided.

Hormones secreted from the adrenal cortex, like cortisone, help the body deal with stress. They regulate sugar metabolism. In doing so they act as a gatekeeper for the flow of energy that glucose ultimately provides to keep the body’s metabolic reactions going efficiently. Cortisone and similar corticosteroids influence virtually every tissue and organ in our body. Cortisone has multiple, far-reaching systemic effects, playing many roles in the body’s effort to carry out its routine processes, maintain internal metabolic harmony or homeostasis, and deal with threats from the person’s physical, emotional and social environment. They are especially involved in mobilising the body’s capacity for self-healing; they are apparently involved in more than two-hundred different clinical disorders.

From the Tibb perspective cortisone, etc., are an integral part of Physis. It plays a critical role in the body’s inflammatory defence against disharmony brought about by infections or malignancies, or by unresolved stress.

Clinically, cortisone has been used for several decades as an effective treatment for a wide range of inflammatory disorders. However, it has to some extent been a victim of its own success; there is,

unfortunately, a substantial and growing degree of cortisone abuse. When taken as a supplement for various reasons, the immediate effect on pain relief, muscle growth and immune suppression may be dramatic. This may be due to the desire to drive through the pain and stiffness in sporting competition, or to the subjective need for it to deal with the various stresses that modern life confers upon us. Unfortunately the perceived benefits are not long lasting, and so the abuse leads inexorably to one or more serious adverse effects. This increasing abuse of cortisone should be one that regulatory authorities are no doubt aware of, and the increasingly urgent need to counteract it.

Further Reading

Adverse reactions to cortisone: http://www.drugs.com/sfx/cortisone-side-effects.html

Roles of cortisone. Online at: www.todaysdietitian.com/newarchives/111609p38.shtml

Effects of elevated cortisone levels: Online at: www.todaysdietitian.com/newarchives/111609p38.shtml

Stress and its management. Online at: www.tibb.co.za/ailments.html

Physis. Online at: www.tibb.co.za/concepts_tibb.html

www.tibb.co.za/research_reviews.html

Tibb Theory & Practice. Online at: www.tibb.co.za/pub_articles.html