THE NORTHERN HOSPITAL

PREDNISOLONE

"The Field of Waterloo", oil on canvas, 1818, Joseph Mallord William Turner, Tate Gallery, London.

"...A damned serious business... the nearest run thing you ever saw in your life".

The Duke of Wellington, after the Battle of Waterloo, 18 June 1815.

"You have to say this about Turner though, he's an equal opportunity pessimist. As much as he wants to see the end of Napoleon, he's got a damned funny way of celebrating Waterloo.

In 1817 does he paint victorious Wellington and his gallant scarlet squares of embattled grenadiers? No, he gives us a carpet of corpses in the blackness. Wives and sweethearts with their babies, pathetically searching the carnage for their loved ones. An apparition of pure hell.

*Rather than glorifying the "Iron Duke", it seems to exemplify one his pithiest verdicts, "the next worst thing to a battle lost, is a battle won". No wonder it wasn't until the **19**80s that this painting was properly displayed.*

Turner's refusal to beat the patriotic drum or wave the flag cost him patrons. But with "The Field of Waterloo" his reach for something profound - a British Art that will act out the suffering of victims. But then Turner knows all about the lot of the common people. He is no "gentleman artist".

He was born and grew up in the filthy back alleys of Covent Garden where every day he rubbed shoulders with the desperate and the destitute. This didn't make his "Waterloo", or any of his historical epics manifestos for revolution - there're bigger, more disturbing than that.

They have washing through them the tragic truth about the powerlessness of ordinary people when faced with atrocity and disaster, people who existed right on the edge…."

Simon Schama, The Power of Art, BBC Television, 2010.

Joseph Mallord William Turner was a child prodigy, the next "big thing" in British Art. As such he was admitted into the Royal Academy at the age of 26 years, having already established himself as the youngest ever exhibiter at the Academy when he was just fifteen years of age! Turner had his fortune made, he could have simply painted the standard pleasure and leisure scenes or done portraits for the "quality", but as Simon Schama writes, the work that smoothed his way into the Royal Academy, "Gulbuddin Castle in Snowdonia" should have put everyone on notice! He would become Britain's conscious, "a thorn in the side of self-congratulation". Not only would Turner's work be disturbingly thought provoking and confronting to the "establishment", in his manner of execution, as a proto-Impressionist, he would also be generations ahead of his time. No wonder that during his lifetime he was scorned in his later years, but today is revered as one of history's greatest ever painters. Amoung the better examples we have of the real Turner is "The Field of Waterloo" of 1818.

The Battle of Waterloo was unimpeachably one of the most decisive battles in history. All Europe stood united against Napoleon in his final stand, after it was thought he had finally been tamed, he had risen again seemingly from the dead. One last titanic effort would be required. History stood at the cross roads of a Europe dominated by an enlightened France or a Europe that would in large part revert to the many of the ways of the Ancien Regime. Napoleon was finally defeated, but things could have easily turned out very differently. In the Duke of Wellington's own words, Waterloo was a "dam close run thing". As the news of Napoleon's defeat spread like the proverbial wild-fire across Europe and to the Americas, celebrations broke out over the defeat of the "tyrant", and nowhere else were the celebrations so joyous as in Britain. Champagne glasses clinked in the salons of Royalty and the high and the mighty. It was Britain's finest hour (to then), she now ruled the waves and stood with Russia and Prussia as the greatest land powers in the world. Britain now stood at the height of Empire.

But how does Turner commemorate the victory? - with a dark and grim scene of the field of Waterloo after the battle. No glorious celebrations, just the dead packed on top of one another, filling the fields to the horizon. We see poignant images of grieving families, widows and sweethearts trying to identify their lost loved ones. Turner showed Britains the real cost of war and it was a scene that struck deep resonance with the ordinary folk and the ordinary soldier. The work was so controversial and shocking, perhaps even 'treasonous", that it would not be properly displayed to the public for well over a one hundred and fifty years! And what of the actual victory over Napoleon? Was Napoleon such a "tyrant"; or was he merely far more successful at what he did than any other general and leader of his time. International relationships were, and had always been simply about the "balance of power". Napoleon's greatest "sin" was in fact that he was simply more successful than any other general of his time, indeed of any time. Waterloo remains one of the great "what ifs" of history. Would a Europe united under France, the most enlightened nation in the old world to have emerged from the "Age of Reason" have really been such a bad thing, compared to the world that did in fact arise.

Napoleon as his recent biographer, the magisterial, Andrew Roberts, so elegantly described was a far more complex man than simply a brilliant general and leader of men, who established the basis of the Code of Law in the West, just as Justinian had so done thirteen centuries previously. He was also a quintessential child of the Enlightenment. He was intensely interested in the latest scientific developments. He held audience with the great scientists of defeated lands, such as Volta in Italy and did them homage. In the Egyptian expedition he brought a small army of scientists, writers and historians with him to study the culture and the natural history of the lands he conquered. Astonishing advances were made in the understanding of the history of these lands including work that led to the deciphering of the Hieroglyphic code. In all likelihood Europe would have been unified fully two centuries before the European Union. And who can tell what advances in the sciences and humanities could have been achieved by a Europe at peace and untied? But the victory over Napoleon left Europe divided and strongly militaristic. Andrew Roberts, tellingly, ponders the legacy of Waterloo, and what might have been; "Who is to say that a Europe dominated in the Nineteenth century by an enlightened France would have been any worse than the one that eventually transpired, in which Prussia dominated Germany and then forced itself onto the continent in ways far less benign than Napoleon?".

Indeed! If Waterloo had have gone Napoleon's way perhaps all of Europe would have been united in a continental "Belle Epoch". Instead the rise of aggressive Prussian militarism would in the long term lead to a somewhat less enlightened unification of Europe that could not possibly have been anticipated by the "victors" of Waterloo - the Third Reich.

When we prescribe the potent anti-inflammatory agent prednisone, we may think to celebrate a great victory over the disease that we treat. But we must remain wary, even the greatest of victories, may have unanticipated costs, both in the short term as Turner most poignantly demonstrated and in the longer, as the magisterial Andrew Roberts, so elegantly elucidated!

PREDNISOLONE

Introduction

Prednisolone is an orally active synthetic corticosteroid.

The precursor agent Prednisone is *activated by the liver* into prednisolone.

Prednisolone exceeds hydrocortisone in glucocorticoid and anti-inflammatory activity, being about three times more potent on a weight basis than the parent hormone, but is considerably less active than hydrocortisone in mineralocorticoid activity.

As a class the glucocorticoids, when used in **supraphysiological** doses, have a large number of adverse effects.

Most of these adverse effects however relate to **long term** treatment and **do not preclude short term use.**

History

Cortisone was first identified by the American chemists **Edward Calvin Kendall** (1886 - 1972) and **Harold L. Mason** while researching at the Mayo Clinic.

Kendall was awarded the **1950 Nobel Prize for Physiology or Medicine** along with **Philip S. Hench** and **Tadeus Reichstein** for the discovery of the adrenal cortex hormones as well as their structures and functions.

Harold. Mason's contributions to the crystallization and characterization of cortisol have generally been forgotten outside of the Mayo Clinic.

Prednisone and prednisolone were introduced into clinical practice in 1955.

Chemistry

Predni**sone** and Predni**solone** are both synthetic corticosteroids but have slightly different chemical structures**.**

Prednisone is *activated by the liver* into prednisolone:

Prednisone itself has no substantial biological effects **until converted via hepatic metabolism to prednisolone**

- Prednisone → prednisolone.

Predni**solone** may therefore be preferred in patients with significant liver disease

Physiology

The principle physiological roles of the corticosteroids are widespread and complex, but essentially fall into three groups:

1. Enhancing the effects of circulating catecholamines

2. Metabolic effects

3. Global suppression of anti-inflammatory and immune responses

At the highest level, the corticosteroids are said to enable and enhance the complex cardiovascular and metabolic "fight or flight" survival responses of the organism to the presence of "stressors"

Classification

Naturally occurring adrenocortical steroids:

The **naturally occurring** adrenocortical steroids are:

- **Hydrocortisone (or cortisol)**
- **Cortisone**

These have both anti-inflammatory (glucocorticoid) and salt retaining properties, ie mineralocorticoid properties).

They are principally used as replacement therapy in adrenocortical deficiency states.

Synthetic corticosteroids:

The **synthetic** corticosteroid compounds include:

- **Prednisolone**
- **Prednisone**
- **Dexamethasone**
- **Methylprednisolone**
- **Fludrocortisone**

These are mainly used for their anti-inflammatory properties.

Classification according to predominant activity:

1. Synthetic agents with *marked glucocorticoid* activity and an *absence* of significant salt-retaining activity:

    - **Dexamethasone**
    - **Prednisolone**
    - **Methylprednisolone**
    - **Betamethasone**

    These drugs are primarily used for their potent anti-inflammatory effects.

2. Synthetic agents with predominant mineralocorticoid activity:

    - **Fludrocortisone**

    It is used as a mineralocorticoid replacement for patients with primary adrenal insufficiency and as a treatment for orthostatic hypotension.

3. Agents with a combination of both *glucocorticoid* activity and mineralocorticoid activity.

    - **Hydrocortisone**

Preparations

Available preparations include:

Tablets: 1 mg, 5 mg, 25 mg.

Oral liquid: 5 mg/mL, in 30 mL bottle.

Mechanism of Action

The corticosteroids **regulate gene expression**.

When a corticosteroid enters a cell, it combines with corticosteroid receptors in the cytoplasm.

This drug-receptor complex enters the nucleus where it controls synthesis of protein, including enzymes that regulate cell activity such as inflammation.

Pharmacodynamics

Effects of the corticosteroids in general include:

1. Glucocorticoid effects including:

    - **Enhancing the vascular sensitivity to circulating catecholamines.**
    - Metabolic effects:
        - ♥ Gluconeogenesis:
            - ♥♥ This is the generation of glucose from *non-carbohydrate* carbon substrates such as pyruvate, lactate, glycerol, and glucogenic amino acids.
        - ♥ Proteolysis
        - ♥ Lipolysis
        - ♥ All corticosteroids can increase calcium excretion
    - Suppression of inflammation and immune responses.

2. Mineralocorticoid effects including:

    - Hypertension
    - Sodium and water retention
    - Potassium loss.

The corticosteroids as a group may have predominantly glucocorticoid effects (e.g. dexamethasone), mineralocorticoid effects (fludrocortisone), or a combination of both (e.g. **hydrocortisone**).

Note that *systemic effects* may result from all of oral, intramuscular, intravenous, inhaled, intra-articular and topical administration.

Pharmacokinetics

Absorption:

- Prednisolone is given orally

Distribution:

- Prednisolone is widely distributed to all body tissues.
- Prednisolone is 90 - 95 % bound to plasma proteins.

Metabolism and excretion:

- Prednisolone has a usual plasma half-life of two to four hours.

Indications

Prednisolone indications include:

1. Acute broncho-inflammatory conditions:

   Corticosteroids are widely used in the treatment of airways disease to reduce bronchial inflammation and hyper-responsiveness.

   - Asthma
   - COPD
   - Croup

2. Allergic conditions:

   Allergic conditions in general, including:

   - Adjunctive therapy in anaphylaxis
   - Serum sickness
   - Insect bites
   - Allergic dermatological conditions

3. Anti-inflammatory effect:

   Prednisolone is used as a general anti-inflammatory agent for a vast range of indication, with variable evidence for this use.

   Conditions include:

   - Gout/ pseudogout, in severe cases are when other agents are contraindicated.
   - Autoimmune dermatological conditions
   - Minor burns/ sunburn for symptomatic relief

3. Immunosuppression:

Corticosteroid in **higher doses** than those used purely for anti-inflammatory effects may be used by appropriate specialists or under their supervision for a large range of rheumatic or autoimmune type conditions, including:

- Inflammatory bowel disease
- Ocular conditions (under strict supervision of an ophthalmologist)
- A large range of rheumatic / connective tissue diseases
- In oncology as a general anti-inflammatory agent
- Some haematological disorders of autoimmune nature
- Some neurological autoimmune conditions, such as Bells' palsy and mild exacerbations of M.S

Contra-indications/precautions

These include:

1. Infections (caution):

   Immunosuppression can increase the risk and severity of infection and so caution is advised when prescribing hydrocortisone in a patient with active or latent infection.

   Some conditions require *both* corticosteroid and control of infection, (e.g. infective exacerbation of COPD or asthma) and this is usually safe so long as the infection can be effectively treated at the same time.

   In general terms, the decision to start or continue corticosteroids in a patient with infection depends on a number of factors including:

   - The type of infection:
     - ♥ Including whether active or latent
     - ♥ **Systemic fungal** infections generally contraindicate the use of corticosteroids.
   - Its severity
   - Whether the infection can be treated or controlled at the same time.
   - The specific indication for hydrocortisone.

2. Live vaccines:

- Administration of live or live attenuated vaccines is contraindicated in patients receiving **immunosuppressive doses** of corticosteroids.

  Killed or **inactivated** vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids, however the response to such vaccines may be diminished.

3. Known hypersensitivity to the excipients.

4. Intra-articular injection (corticosteroids in general):

   - Corticosteroids are contraindicated in patients with infective arthritis, skin or soft tissue infections near joint (risk of introducing bacteria into joint) or a prosthetic joint.

*The following **precautions** do not apply when used at **physiological doses for adrenal insufficiency**:* [2]

5. Latent TB:

   - May be reactivated; consider treatment with isoniazid.

6. Peptic ulcer disease:

   - Corticosteroids may increase the risk of peptic ulcers.

7. Diabetes:

   - Corticosteroids (including intra-articular injections) may cause hyperglycaemia and worsen diabetes control.

8. Hypertension/ heart failure:

   - May be worsened due to sodium and water retention (mineralocorticoid effect).

9. Psychiatric disorders:

   - May be exacerbated.

10. Glaucoma:

    - Intraocular pressure may increase.

11. Osteoporosis:

- Long-term corticosteroid use increases the risk of osteoporotic fractures and accelerates bone loss.

12. Myasthenia gravis:

- Increased muscle weakness may occur during the first few weeks of treatment with corticosteroids; (seek specialist advice).

Pregnancy

Prednisolone is a category A drug with respect to pregnancy.

Category A drugs are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Note that **hydrocortisone, prednisolone, prednisone** and **methylprednisolone** are the preferred agents for maternal disorders as placental transfer is limited, while **betamethasone** and **dexamethasone** are the preferred agents for fetal disorders as placental transfer is greater. [2]

Breast feeding

Prednisolone is safe in pregnancy.

Adverse Effects

Adverse effects are an inevitable result of **systemic** corticosteroid treatment if the **dose and/ or duration** of treatment are sufficient, because most are dose-related biological effects of the hormone.

Short courses of high dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

The *longer - term* adverse effects of corticosteroids *in general* include:

Adverse glucocorticoid effects:

1. Adrenal suppression

   Manifests with longer term exogenous administration when:

   - Therapy is **abruptly ceased**

   Or

- When a **stressor occurs**; due to secondary adrenocortical and pituitary unresponsiveness, particularly in trauma, surgery, infection or illness

Adrenal hypofucntion can lead to Shock/ increased risk of shock states.

The hypothalamic-pituitary-adrenal axis is suppressed by glucocorticoid therapy.

The dose, duration of treatment and individual patient characteristics affect the onset and extent of this effect.

Treatment with **prednisolone** at doses **greater than 10 mg** (or equivalent dose of glucocorticoid) **daily for more than three weeks** can be considered sufficient to cause clinically significant adrenal suppression that requires glucocorticoid replacement at a time of intercurrent illness, trauma or surgical stress. [1]

Therefore, in this situation, tapering of the glucocorticoid dose is required to avoid both adrenal insufficiency and the rebound in symptoms that may occur with sudden cessation.

After long-term use (more than 2 weeks), dose reduction must be slow to enable the hypothalamic-adrenal feedback system to re-equilibrate.

2. Immunosuppression:

- Increased risk of infection.

- Infections are more common in people treated with supraphysiological doses of corticosteroids, due to immunosuppressive effects.

- **Corticosteroids may also mask the early symptoms and signs (by suppressing the inflammatory repose) of infection, resulting in later diagnosis, delay in treatment, and more severe clinical consequences.**

- Reactivation of *Mycobacterium tuberculosis* infection occurs with such frequency that before commencing immunosuppressant treatment with corticosteroids, screening for active or latent tuberculosis (TB) should be considered.

- Prophylaxis for *Pneumocystis jiroveci (carinii)* infection should be considered in patients who are at risk and taking high dose oral corticosteroids long term.

3. Metabolic effects:

- Hyperglycaemia:

- ♥ Hyperglycaemia may accompany treatment with corticosteroids, particularly when higher doses are used, and blood glucose concentrations may require monitoring.

- Hypertriglyceridaemia
- Weight gain/ redistribution of fat centripetally, leading to the development of a "Cushingoid" state.
- All corticosteroids increase calcium excretion

4. Dermatological effects:
   - Skin atrophy leading to thin fragile skin.
   - Purpura/ ecchymoses
   - **Poor wound healing**
   - Striae
   - Hirsutism
5. Gastrointestinal effects:
   - Dyspepsia
   - Peptic ulceration
   - Gastrointestinal bleeding
6. Myopathy:
   - Steroid myopathy with muscle weakness/ loss of muscle mass.
   - Tendon rupture can also occur, particularly of the Achilles tendon
7. Bone effects:
   - Osteoporosis:
     - ♥ **Bone density loss** leading to osteoporosis is a risk for patients on continuous (> one month) corticosteroid therapy in doses greater than the equivalent of prednisolone **5 to 7.5 mg per day** or who are receiving frequent pulses of corticosteroid.
     - ♥ It can occur in men as well as women.

- ♥ The risk of osteoporosis becomes greater at higher glucocorticoid doses.

- ♥ Loss of bone mineral density occurs rapidly after corticosteroids are commenced and may exacerbate the osteoporosis associated with some rheumatological diseases, such as ankylosing spondylitis, and inflammatory bowel disease.

- Avascular (ischaemic) necrosis:

  - ♥ Most typically of the of the proximal femoral and humeral head

  - ♥ It is infrequent

  - ♥ It is idiosyncratic (ie unpredictable).

  - ♥ It occurs more commonly following exposure to doses in excess of **20 mg** per day prednisolone (or equivalent dose of other corticosteroid).

  - ♥ The time between corticosteroid exposure and the development of avascular necrosis is variable, and can be up to *many years*, which makes diagnosis difficult.

  - ♥ Avascular necrosis should be considered in the differential diagnosis of hip and groin pain especially in patients who have been on high-dose and/or long-term corticosteroids at any time.

  - ♥ Both the pathogenesis and treatment of this condition remain controversial.

8. Ocular effects:

   - Increased intraocular pressure

   - Cataracts

9. Growth retardation in children:

   - Chronic use of corticosteroids (at pharmacological doses) may retard growth in children.

   - Follow growth and development carefully

   - Catch-up growth may occur after corticosteroid withdrawal.

10. Menstrual irregularities:

- Principally amenorrhoea

11. Psychiatric disturbances:

    - Euphoria
    - Depression
    - Paranoid psychosis

    Note that preexisting emotional instability or psychotic tendencies may also be *aggravated* by corticosteroids.

Adverse mineralocorticoid effects:

1. Sodium retaining effects:

    - Oedema
    - Hypertension

2. Hypokalaemic alkalosis.

Note that most of the adverse effects relate to long term treatment and do not preclude *short* term use.

Corticosteroids applied topically can also cause adverse effects

Dosing

Exact dosing and the duration of dosing depend on the condition being treated as well as the severity of the condition and illness.

See individual conditions and latest Therapeutic Guidelines for full prescribing details.

In general terms:

The initial adult dosage may range from 20 to 100 mg daily, depending on the disease being treated as well as its severity.

In general, the **lowest dose possible** to achieve the desired clinical response should be used.

Low doses are used to produce an **anti-inflammatory effect**, while **higher doses** are needed to produce **immunosuppression**

Prednisone is generally given as **a single daily dose** in the morning to mimic the natural corstisol peak.

Treatment with **prednisolone** at doses **greater than 10 mg** (or equivalent dose of glucocorticoid) **daily for more than three weeks** can be considered sufficient to cause clinically significant adrenal suppression that requires glucocorticoid replacement at a time of intercurrent illness, trauma or surgical stress. [1]

In long term therapy, alternate day dosing can help reduce side effects, as reduce the degree of adrenal suppression which occurs. However, some patients may require daily glucocorticoid therapy because symptoms of the underlying disease cannot be controlled by alternate day therapy.

Use of steroid sparing drugs:

When corticosteroids are required for longer term use, drugs from other classes may be used to allow a reduction of the corticosteroid dose.

For example, in rheumatology, use of disease modifying anti-rheumatic drugs (DMARDs) and NSAIDs often allows a lower corticosteroid dose to be used.

Appendix 1

Approximate relative potencies and half-lives of the glucocorticoids:

Glucocorticoid	Relative glucocorticoid potency	Equivalent dose for glucocorticoid effect	Estimated biological half-life
Hydrocortisone	1	20 mg	8 to 12 hours
Cortisone acetate	0.8	25 mg	8 to 12 hours
Dexamethasone	25 to 50	400 to 800 micrograms	36 to 54 hours
Prednis(ol)one	4	5 mg	18 to 36 hours
Methylprednisolone	5	4 mg	12 to 36 hours

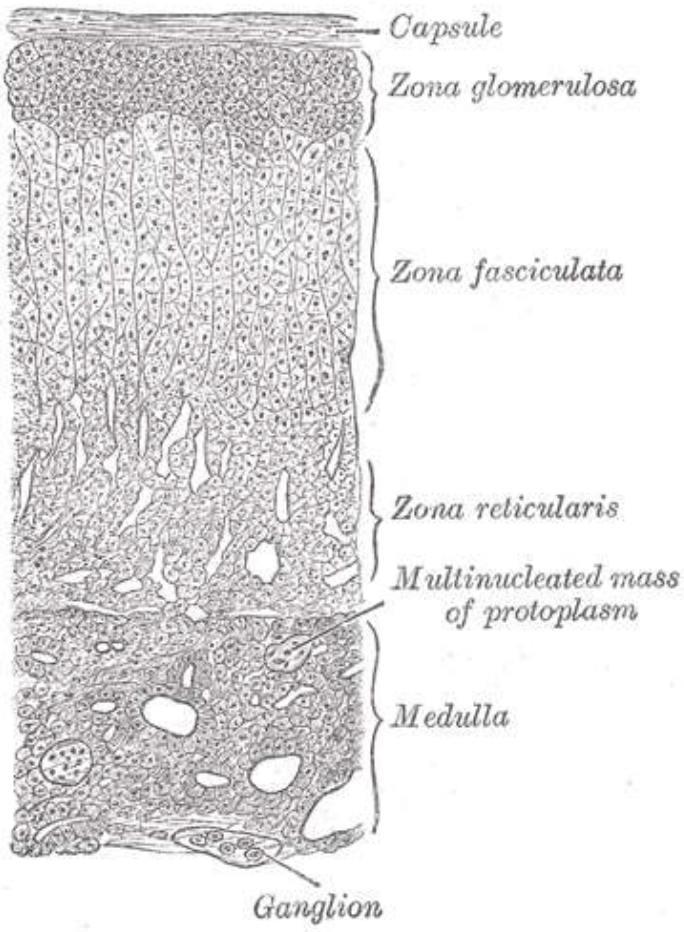
Appendix 2

Relative potencies of the topical preparations of the corticosteroids:

Mild	
Desonide	0.05%
Hydrocortisone	0.5%, 1%
Hydrocortisone acetate	0.5%, 1%
Moderate	
Betamethasone valerate	0.02%, 0.05%
Clobetasone butyrate	0.05%
Methylprednisolone aceponate	0.1%
Triamcinolone acetonide	0.02%
Potent	
Betamethasone dipropionate	0.05%
Betamethasone valerate	0.1%
Mometasone furoate	0.1%
Triamcinolone acetonide	0.1%
Very potent	
Betamethasone dipropionate	0.05% in optimised vehicle
Clobetasol propionate	0.05%

Appendix 3

Physiology of the Adrenal Gland:



Cross sectional anatomy of the adrenal gland, (Gray's Anatomy 1918).

The Adrenal Cortex:

This consists of **3 zones**:

- Zona glomerulosa:
  - ♥ This layer is the main site for production of the **mineralocorticoid** hormone, **aldosterone.**
- Zona fasciculata:
  - ♥ This layer is the main site for production of the **glucocorticoids** (mainly **cortisol**).

- Zona reticularis:

    - ♥ This layer is the main site for production of **androgens**; mainly dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and androstenedione (the precursor to testosterone) in humans.

The Adrenal Medulla:

- The chromaffin cells of the medulla are the body's main source of the circulating catecholamines; **adrenaline** (80 %) and **noradrenaline** (20 %).

"The Field of Waterloo", oil on canvas, 1818, Joseph Mallord William Turner, Tate Gallery, London.

<u>References</u>

1 eTG - November 2015

2. Prednisolone in Australian Medicines Handbook, Accessed February 2015

3. Prednisolone in MIMs 1 August 2011.

Dr J. Hayes
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