Chapter 7 Autoimmune glandular disorders, with special reference to APS and hypoadrenalism (Addison's disease)

I watch the sunrise
lighting the sky
casting its shadows near.
And on this morning
bright though it be
I feel those shadows near me.

But you are always close to me
following all my ways.
May I be always close to you
following all your ways, Lord.

I watch the sunlight
shine through the clouds,
warming the earth below.
And at the mid-day, life seems to say:
'I feel your brightness near me.'

For you are always…

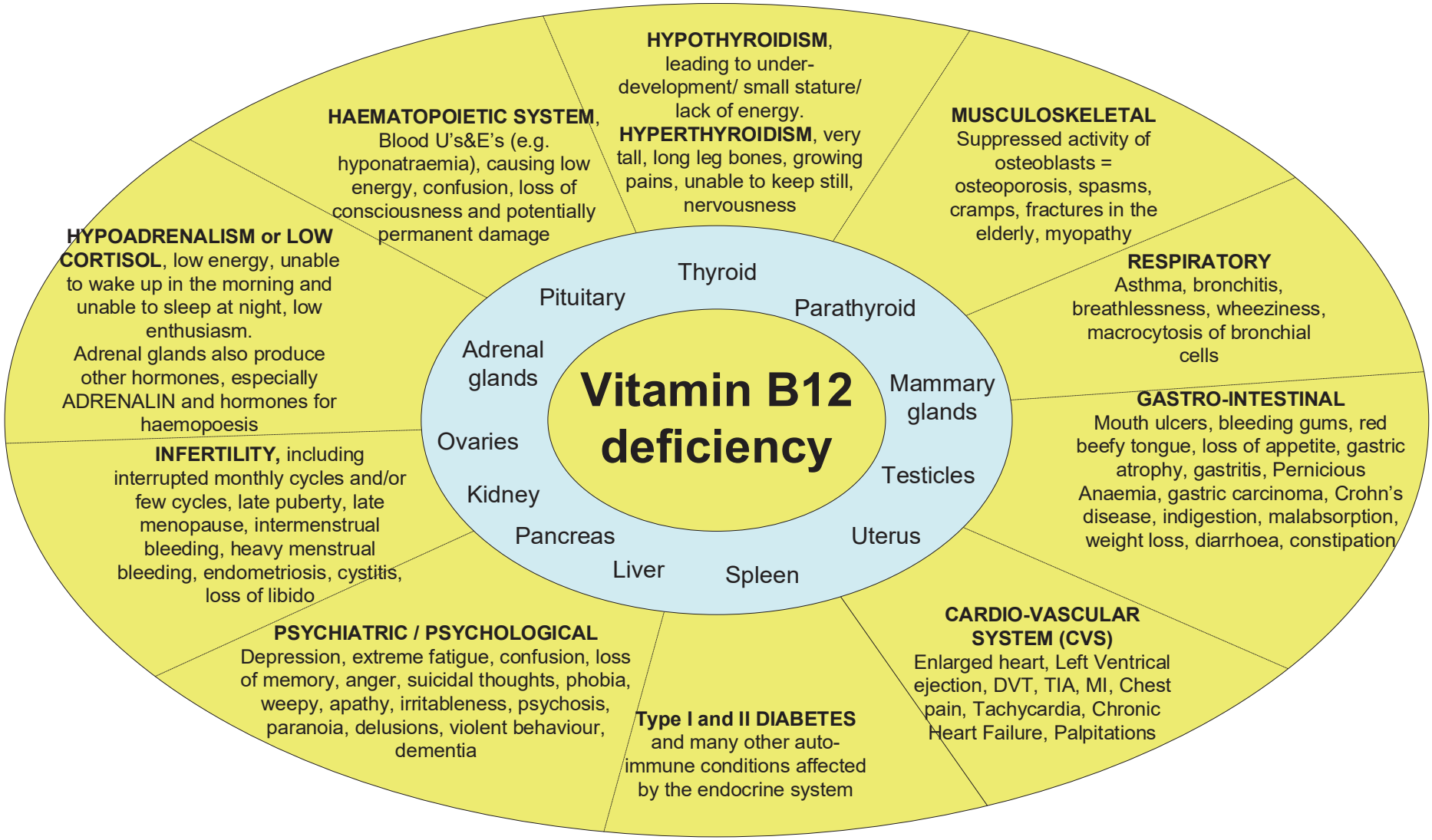
I watch the sunset
fading away,
lighting the clouds with sleep.
And as the evening closes its eyes
I feel your presence near me.

For you are always…

I watch the moonlight
guarding the night,
waiting till morning comes.
the air is silent, earth is at rest
only your peace is near me.

John Glynn

Figure 7-1 Visual Reference Diagram: Vitamin B12 and the endocrine glands



SECTION 1 Autoimmune glandular disorders and vitamin B12 deficiency

In treating vitamin B12-deficient patients over many years we noticed that a significant number of them also suffered from autoimmune glandular disorders. Prominent among these illnesses were the life-threatening condition of hypoadrenalism[32] (under-active adrenal glands) and hypothyroidism (under-active thyroid gland). These patients also had other autoimmune glandular conditions such as diabetes, vitiligo, premature ovarian failure, hyper/hypo parathyroidism and others.

For instance, in 2015, in a total of 1,036 vitamin B12-deficient patients in our Practice, 366 had hypothyroidism (Chandy, 2015). We also had 15 patients with hypoadrenalism (Table 7-1), out of a total Practice population of 5,760 (a much higher incidence of hypoadrenalism than the figure given in *Harrison's Principles of Internal Medicine* of 5 patients in 10,000 in the general population (Arlt, 2012; 2018, p. 2733)). Fourteen of these also had vitamin B12 deficiency and nine had severe hypothyroidism.

Table 7-1 Prevalence of vitamin B12 deficiency and myxoedema among patients with hypoadrenalism, 1981-2015

Name (some names withheld to preserve anonymity)	Sex	Hypoadrenalism	Myxoedema (severe hypothyroidism)	B12 deficient
Angela Abraham	Female	Yes	No	Yes
Patient A	Female	Yes	Yes	Yes
Patient B	Female	Yes	No	Yes
Leanne Walker (née Chandy)	Female	Yes	No	Yes
Lisa Henderson	Female	Yes	Yes	Yes
Joan Richardson	Female	Yes	Yes	Yes
Patient C	Female	Yes	Yes	Yes
Patient D	Male	Yes	No	Yes
Donna Lawton	Female	Yes	Yes	Yes
Patient E	Male	Yes	No	Yes
Donna Kennedy	Female	Yes	Yes	Yes
Patient F	Male	Yes	Yes	Yes
Patient G	Male	Yes	Yes	No
Patient H	Female	Yes	Yes	Yes
Patient I	Female	Yes	No	Yes
Total ratio		**15/15**	**9/15**	**14/15**

Note: Shinwell Medical Practice Population (SMP) = 5,760 patients
Total number of patients on levothyroxine (for underactive thyroid): 366 (Male: 82; female: 284).
Prevalence of hypoadrenalism in the SMP – 15 patients out of 5,760 (much higher incidence than the figure given in *Harrison's Principles of Internal Medicine* of 5 patients in 10,000 in the general population (Arlt, 2018).

Of those with hypoadrenalism, 9/15 also have severe hypothyroidism (χ^2=1500, df=1, p=0.00) and 14/15 also have diagnosed B12 deficiency (χ^2=58, df=1, p=0.00), showing a strong correlation.

[32] Hypoadrenalism is also known as adrenal insufficiency or Addison's disease (after Thomas Addison who gave the first clinical description of the condition in 1855).

Glands produce hormones which are essential for regulation of all body activities. Groups of glandular disorders occurring together can produce devastating effects and a host of diverse symptoms which vary from patient to patient.

7.1 Vitamin B12 deficiency – an underlying cause?

We observed that, if untreated, these conditions became progressive (moved from one gland to another) which suggested to us that there was an underlying cause which was likely to be vitamin B12 deficiency. To our knowledge we are the first to suggest this, although many researchers have noted the frequent occurrence of autoimmune glandular disorders, and other autoimmune conditions, in B12-deficient patients. For instance, autoimmune hypothyroidism has been found to be prevalent in patients with vitamin B12 deficiency (Issac et al., 2015; Morel et al., 2009; Ness-Abramof et al., 2006).

Our hypothesis that vitamin B12 deficiency was implicated in these glandular disorders was vindicated because our patients recovered well when treated with vitamin B12 alongside the relevant hormone replacement *without the need for an elaborate complex of drugs*. The results were dramatic and patients' symptoms improved much more sharply than with hormone-replacement therapy alone. Although our patients would mostly need to remain on this combined treatment for life, the vitamin B12 appeared to effect some glandular repair; the disease progression was stopped and the patients' quality of life greatly improved.

7.2 Need to screen for autoimmune glandular conditions in B12-deficient patients

In view of the above, this chapter aims (in Section 1) to alert clinicians to the importance of screening for autoimmune glandular disorders in vitamin B12-deficient patients. Its second aim, in Section 2, is to share expertise in the diagnosis and treatment of hypoadrenalism in particular. This is a serious illness which frequently co-occurs with vitamin B12 deficiency but is easy for the clinician to miss as its symptoms, such as dizziness, leg pain, blurred vision and breathlessness, may be unspecific. Many patients with hypoadrenalism are still today not diagnosed until an emergency arises (Leelarathna et al., 2009). Because of the co-occurrence of hypoadrenalism with vitamin B12 deficiency, we developed some expertise in its diagnosis. Unfortunately, we found the current clinical guidelines inadequate for diagnosing and treating this condition, so we developed our own (given in full in Appendix 2 at the end of this book). We hope that by sharing this knowledge we will contribute to ensuring prompt diagnosis of patients with this condition.

The last part of the chapter, Section 3, gives a brief overview of the relationship of vitamin B12 deficiency to other autoimmune glandular disorders.

7.3 Autoimmune Polyglandular Syndrome

The condition described above in which a person suffers from multiple autoimmune glandular disorders at the same time is called Autoimmune Polyglandular Syndrome (APS).[33] It was classified in the 1980s into Types I, II, III and IV according to the pattern of glands involved (see Box 7-1) (Neufeld & Blizzard, 1980; Neufeld et al., 1980; Tincani et al., 2008). Since then, further discoveries have widened the classification.

[33] APS is also known as Polyglandular Autoimmune Syndromes or Polyendocrine Autoimmune Syndromes: not to be confused with anti-phospholid syndrome which has the same acronym.

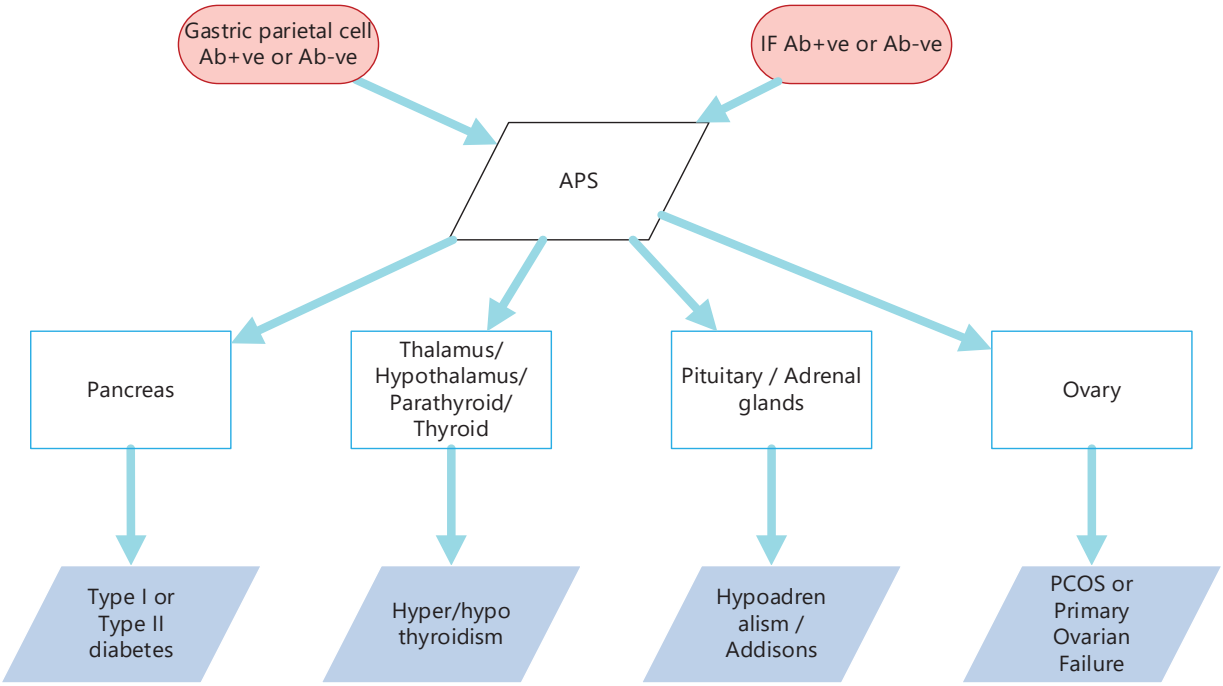
Box 7-1 Types of APS

APS TYPE I is very rare. It is an inherited disorder (involving mutation of the AIRE gene) with prevalence ranging between 1 in 9,000 in susceptible communities to 1 in 80,000 (Betterle et al., 2002). It has three main component diseases: chronic candidiasis (affecting the skin, nails, tongue, mucous membranes); chronic hypoparathyroidism (affecting calcium and phosphorus levels – leading to muscle cramps, spasms and seizures), and **autoimmune Addison's disease (described in detail below).**
APS TYPE II (also known as Schmidt's Syndrome) combines autoimmune Addison's disease with autoimmune thyroid disease (Hashimoto's thyroiditis). It can also include a range of other autoimmune disorders, such as Type I diabetes mellitus, hypoparathyroidism, vitiligo, PA/vitamin B12 deficiency and gonadal failure.
APS TYPE III groups thyroid autoimmune diseases and other autoimmune diseases (but excludes autoimmune Addison's disease, hypoparathyroidism and chronic candidiasis). It can be associated with diabetes mellitus, PA/vitamin B12 deficiency, vitiligo, alopecia, hypogonadism, myasthenia gravis and rheumatoid arthritis, among others.
APS TYPE IV covers other associations of autoimmune conditions, such as Addison's disease with hypogonadism, PA/vitamin B12 deficiency, vitiligo, alopecia, hypophysitis, but excludes chronic candidiasis, hypoparathyroidism, thyroid autoimmune diseases and type 1 diabetes mellitus.

Often, at least three glands are affected but researchers have counted up to 150 different autoimmune illnesses in patients suffering from this condition (Betterle et al., 2002, p. 338). These include, as mentioned above, hypoadrenalism and hypothyroidism but also diabetes mellitus, myasthenia gravis (weakness and muscular fatigue), coeliac disease (inflammation of the small intestine), hypo/hypergonadism (disorder of sex hormones), alopecia, pernicious anaemia, vitiligo (absence of skin pigment), autoimmune chronic active hepatitis, lymphocytic hypophysitis (autoimmune disease of the pituitary gland) and many others.

APS is considered to be a rare condition, but our experience suggests that APS Types II and III are more common than generally thought. This may be because autoimmune glandular disorders are often treated by the medical profession as isolated conditions, independent of one another, so APS is not being diagnosed and therefore an underlying cause (such as vitamin B12 deficiency) is not being sought. In a Practice population of 5,760 patients we had nine patients suffering from autoimmune hypoadrenalism with autoimmune thyroid disease (Table 7-1), therefore fulfilling the criteria for APS Type II. Eight of these were also vitamin B12 deficient. We also had patients suffering from APS Type III, with combinations of disorders including, for example, underactive thyroid and alopecia. Several cases in this chapter (Cases 7-1, 7-3, 7-5, 7-6, 7-7) are examples of patients suffering from a combination of autoimmune conditions with vitamin B12 deficiency.

Figure 7-2 Autoimmune progressive damage



Graphic by Hugo Minney

7.4 Treatment of APS and importance of early detection

The standard approach to treating glandular disorders is to treat each disorder separately. In our experience, misdiagnosis is common. Patients may be inadvertently misdiagnosed as suffering from Myalgic Encephalopathy (ME), Chronic Fatigue Syndrome (CFS), fibromyalgia (FM), depression or even Multiple Sclerosis (MS) (which cannot be treated: the medications only alleviate symptoms), when the correct diagnosis should be vitamin B12 deficiency/APS (hypoadrenalism), which can be treated and cured.

Case 7-1 Vitamin B12 deficiency with two autoimmune conditions

Tracey Baldam (born 1969) initially presented with many of the signs and symptoms of vitamin B12 deficiency 15 years earlier – the blood test showed that she had both vitamin B12 deficiency and underactive thyroid. A few years ago she stopped treatments for both conditions herself. Shortly afterwards she presented with classic rheumatoid arthritis symptoms: swollen painful joints. She did not make the connection between stopping the treatment and the pain. Diagnosis of rheumatoid arthritis was made by hospital consultants who commenced her on methotrexate.

As she was still in a lot of pain with swollen joints, she presented to our surgery. We suggested she should go back on vitamin B12 injections and thyroxine. Within three months (by August

2011) she had totally recovered and herself stopped the methotrexate (an immune-system suppressant).

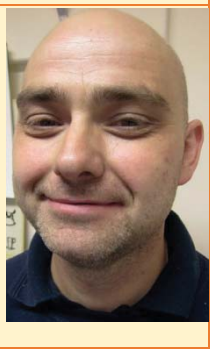
Many patients with depressed (or hypo-) function in one gland have evidence of other endocrine gland dysfunction; therefore it is important for the clinician to be alert to the possibility of combinations of conditions. Where the doctor does recognise a progression of autoimmune glandular disorders, classical medicine concludes that the progression cannot be stopped and fails to see that simple treatment can resolve or alleviate these conditions. Alongside the standard treatments, we would recommend vitamin B12 therapy which, in our experience, appears to help to correct dysfunction of the HPA Axis (see Figure 7-3 below). As with many conditions, early detection and prompt effective action can prevent irreversible end-stage crisis presentation.

7.5 Vitamin B12 – the link with autoimmunity

Autoimmune disorders result from the body's immune system mistakenly attacking its own cells instead of invading pathogens. The incidence of autoimmune disease worldwide is increasing, especially in developed countries, and is estimated to affect 3% or more of the world population (Bolon, 2012). Autoimmunity can occur in any body system or tissue and dozens of different conditions have been identified.

How may vitamin B12 deficiency be linked to autoimmunity? There is evidence that vitamin B12 may play a general role in preventing autoimmune attack. Researchers have shown that vitamin B12 strengthens the body's immune systems. A Japanese team, for example, found that vitamin B12 injections increased the number of $CD8^+$ T cells that fight infection: "We conclude that vitamin B12 acts as an immunomodulatory for cellular immunity" (Tamura et al., 1999). In this connection it can be noted that CD8+ T-cell deficiency is a feature of many chronic autoimmune diseases (Pender, 2012). Others have found that vitamin B12 "has important immunomodulatory effects on cellular immunity, and abnormalities in the immune system in pernicious anaemia are restored by B12 replacement therapy" (Erkurt et al., 2008). An example from our own Practice of a patient suffering from these effects is given in Case 7-2.

Case 7-2 Common immunodeficiency



Douglas Stephenson presented in 2007 (aged 37) with recurrent infections and bronchiectasis. On referral, the hospital diagnosed immunodeficiency and commenced immunoglobulin treatment.

In May 2013, we identified low blood serum B12 of 140 ng/L, and commenced treatment. By July 2013 he reported to the immunology clinic that he was very well, suffered no more infections and no diarrhoea. Blood tests confirmed no proteinuria, although vitamin D supplementation is still required.

7.6 Overview: glands, hormonal cycles and the HPA axis

This sub-section is included for the benefit of the general reader to explain how the glandular system is interlinked and therefore how cumulative and progressive effects may occur.

The human body secretes and circulates about 50 different hormones (chemicals) from nine specialised glands (the pituitary, the thyroid, the four parathyroids, the two adrenals and the thymus) and several organs which can produce hormones (including the pancreas, heart, kidneys, ovaries, testicles and intestines). For example: the pancreas secretes insulin which regulates glucose metabolism; the thyroid gland secretes thyroxine (T4) and triiodothyrone (T3) which regulate metabolism and growth; and the adrenal cortex secretes glucocorticoids (cortisol), mineralocorticoids (aldosterone) and androgens. Cortisol stimulates glucose synthesis and anti-stress and anti-inflammatory processes. Aldosterone affects the sodium/potassium balance (Society for Endocrinology, 2018).

Hormones are released by the glands or organs directly into the intercellular fluid and carried through the bloodstream to target organs. They carry messages which control many body processes such as metabolism (energy levels), homeostasis (internal balance of body systems, such as temperature), reproduction, response to stress, and contraction of muscles.

The entire network is controlled by the hypothalamus (part of the brain) and the pituitary gland (at the base of the brain and which has two parts: the anterior and the posterior). The hypothalamus is the link between the hormonal and nervous systems. It receives messages through the nerves (such as the presence of daylight or heat and cold) and produces hormones in response to these stimuli. Some of these hormones stimulate other glands. The hypothalamus is important for regulating heart rate, blood pressure, body temperature, fluid and electrolyte balance, appetite and weight, glandular secretions of the stomach and intestines, sleep cycles and stimulation of the pituitary gland (Sargis, 2015). The pituitary also in turn secretes several hormones which act on other endocrine glands.

To function properly, all hormone-producing glands must release the correct amount of hormones at the right time. Many hormones are cyclical, with the cycle (circadian rhythm) ranging from a whole lifetime to a single day. For example, in a healthy human the level of cortisol begins to rise just before waking up, peaks at midday and reduces at night when the body needs rest (Chart 7-1). When a gland or the HPA axis malfunctions, hormonal disturbances occur.

Different amounts of hormone are needed at different times. In general terms, and for most of the cyclical hormones (those responsible for growth, fertility, circadian activity, etc.) the pattern is (see Figure 7-2):

- the brain informs the **hypothalamus** how much hormone should be present for a particular purpose (e.g. wakefulness, fight or flight, etc.);
- the **hypothalamus** informs the **pituitary** which checks this against current levels;
- if more hormone is needed, then the **pituitary** stimulates the appropriate hormone-producing gland (endocrine organ). The pituitary is too delicate and complex to produce the quantities of hormone needed, but can produce small quantities of the **stimulating hormones**.

Chart 7-1 Cortisol daily cycle (circadian rhythm) in a healthy human

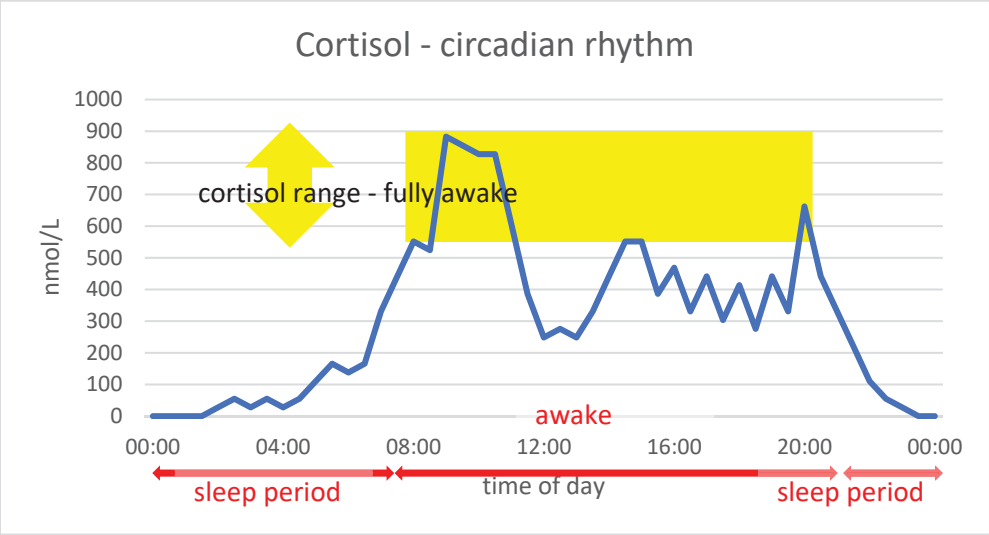
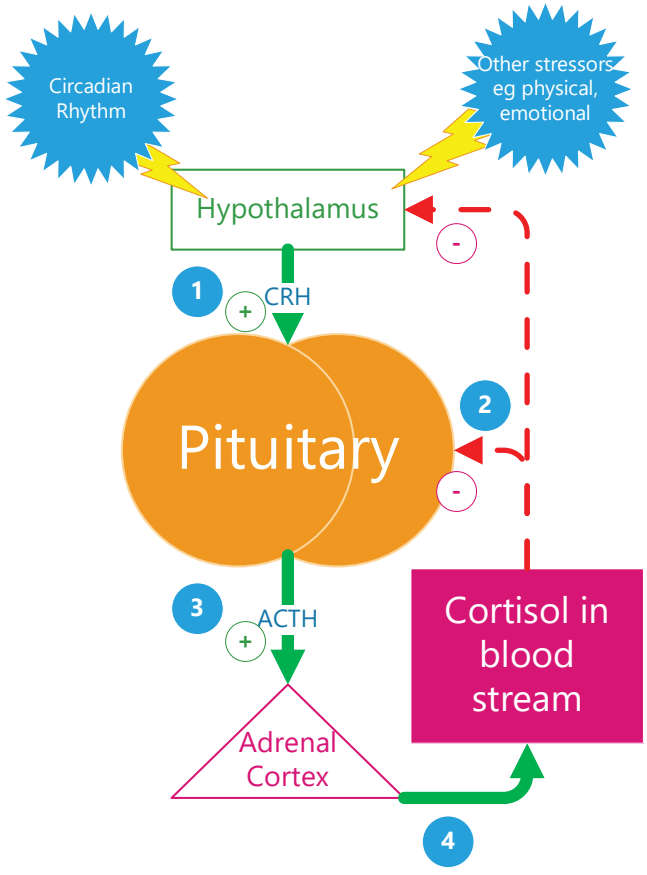


illustration by Hugo Minney

So, to break this into stages (using the example of cortisol):



Graphics by Hugo Minney

Figure 7-3 The hypothalamic-pituitary-adrenal (HPA) axis

(1).The brain sends a signal via a nerve impulse to the hypothalamus (the brain can see whether it is daylight, whether there is danger, whether food is required and so on). The hypothalamus converts it to a chemical signal (that is, it produces a Corticotropic Releasing Hormone or CRH) to send to the pituitary to convey the information.

(2) and (3).The pituitary checks the current hormone level and if more is required, sends an AdrenoCorticoTropic Hormone (ACTH), that is a stimulating hormone, to the adrenal glands.

(4) The endocrine gland that produces cortisol is the adrenal cortex (the outer layer of the adrenal gland, also known as the suprarenal gland).

SECTION 2: APS component illnesses: Hypoadrenalism

Hypoadrenalism, a disorder in which the adrenal glands do not produce enough steroid hormones, is also called "Addison's disease" after Thomas Addison (1793-1860), who gave the first clinical description of the condition. An interesting point here is that even at this early date Addison noticed that the adrenal glands were damaged in all the 11 cases of pernicious anaemia (PA) on which autopsies were performed at that time (Graner, 1985; Pearce, 2004). In other words, he had spotted a connection between vitamin B12 deficiency (manifested in the form of PA) and glandular damage. Addison at first thought that hypoadrenalism was a cause of PA but later abandoned this idea (Addison, 1855). As we now know, PA induces vitamin B12 deficiency and may in fact itself be an end-stage presentation of B12 deficiency – see Chapter 4 of this book, so we believe it may have been the other way round: that is that vitamin B12 deficiency in PA had led to hypoadrenalism in Addison's patients.

Case 7-3 Importance of timely intervention in hypoadrenalism

Donna Kennedy, a hospital nurse, was diagnosed with vitamin B12 deficiency (with a B12 blood level of 248 ng/L in 2012) but initially did not follow any treatment. She attended the surgery in August 2013 with a red rash as shown in the photo. An allergic reaction was initially suspected but her cortisol level was 130 nmol/L (normal range 500-700 in the morning) and B12 level 243 ng/L (normal range 350-900 ng/L), which, in conjunction with extreme fatigue and breathlessness, confirmed vasculitis rather than urticaria. Emergency treatment was given before the cortisol results were known which proved to be the correct treatment. Donna was given B12-replacement therapy (injections on alternate days), along with oral hydrocortisone short-term to treat the transient hypoadrenalism and skin rash. Through this treatment her normal adrenal function was restored, indicating that this timely intervention had prevented long-term damage to the adrenal glands. She recovered completely and returned to her nursing duties.

Hypoadrenalism leads to multiple health problems resulting from under-production of the three types of hormone secreted by the adrenal cortex. These include (from the Society for Endocrinology (2018)):

- **Glucocorticoids**: Mainly cortisol, which is important for the body's response to stress, (including illness), for regulating metabolism, for stimulating glucose production and in anti-inflammatory processes.
- **Mineralocorticoids:** Mainly aldosterone, which is important for maintaining salt and water levels which regulate blood pressure.
- **Adrenal androgens**: Sex hormones (small amounts of oestrogen, testosterone, progesterone and dehydroepiandrosterone (DHEA)). DHEA is important for energy levels.

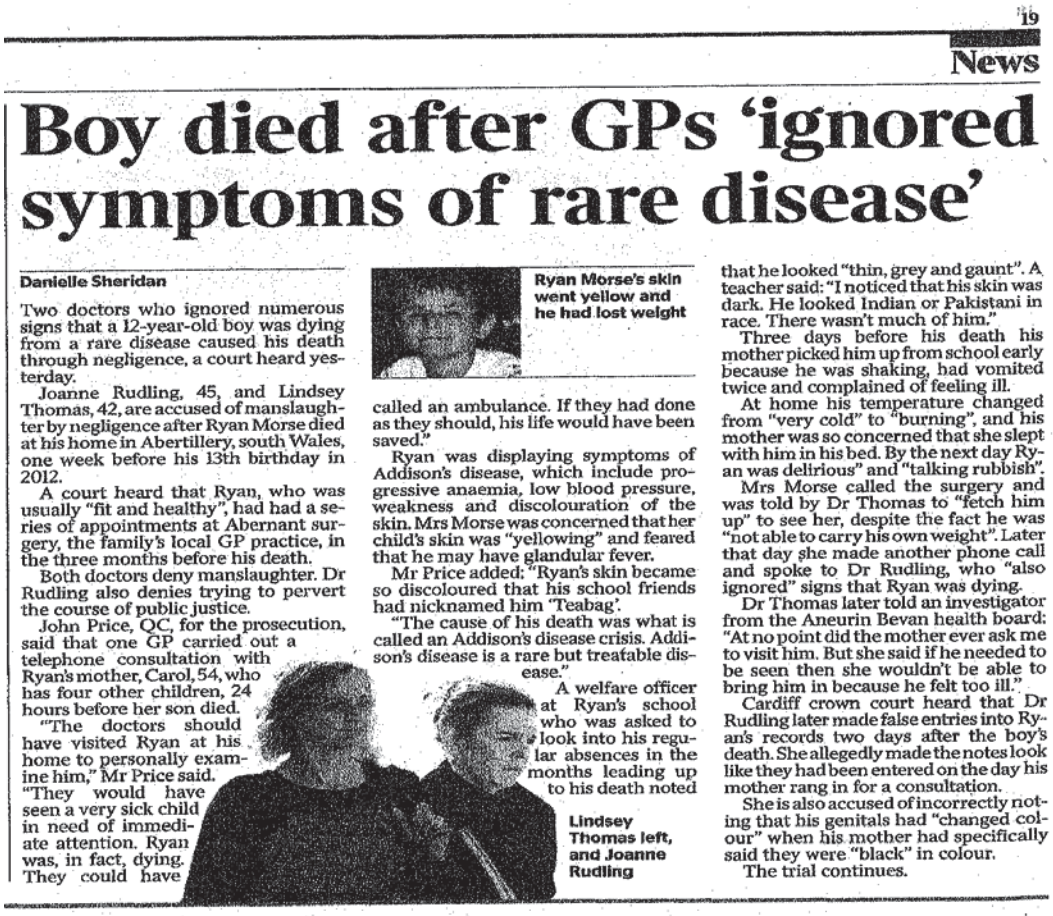
7.7 Forms of hypoadrenalism

There are three forms of the disease (primary, secondary and tertiary) depending on the cause of the disorder. Treatment depends on the form diagnosed. Unfortunately, hypoadrenalism is often

undiagnosed until the crisis point is reached, where the adrenal glands are almost totally destroyed. Known as "Addisonian crisis", this condition can be fatal (see Figure 7-4 and Case 7-4).

This illness can occur as part of APS or on its own (as an isolated condition) (Arlt & Allolio, 2003). By definition, it is included in APS Types I and II and may also feature in Type IV. Through our work with B12-deficient patients in whom extreme fatigue was prevalent, we discovered that low cortisol – a result of under-active adrenal glands - was also contributing to their symptoms. In the absence of satisfactory diagnostic guidelines, this led us to develop our own diagnostic Protocol (Appendix 2) for capturing this condition in the early stages.

Figure 7-4 Newspaper report: Death from undiagnosed Addison's disease



19

News

Boy died after GPs 'ignored symptoms of rare disease'

Danielle Sheridan

Two doctors who ignored numerous signs that a 12-year-old boy was dying from a rare disease caused his death through negligence, a court heard yesterday.

Joanne Rudling, 45, and Lindsey Thomas, 42, are accused of manslaughter by negligence after Ryan Morse died at his home in Abertillery, south Wales, one week before his 13th birthday in 2012.

A court heard that Ryan, who was usually "fit and healthy", had had a series of appointments at Abernant surgery, the family's local GP practice, in the three months before his death.

Both doctors deny manslaughter. Dr Rudling also denies trying to pervert the course of public justice.

John Price, QC, for the prosecution, said that one GP carried out a telephone consultation with Ryan's mother, Carol, 54, who has four other children, 24 hours before her son died.

"The doctors should have visited Ryan at his home to personally examine him," Mr Price said. "They would have seen a very sick child in need of immediate attention. Ryan was, in fact, dying. They could have called an ambulance. If they had done as they should, his life would have been saved."

Ryan was displaying symptoms of Addison's disease, which include progressive anaemia, low blood pressure, weakness and discolouration of the skin. Mrs Morse was concerned that her child's skin was "yellowing" and feared that he may have glandular fever.

Mr Price added: "Ryan's skin became so discoloured that his school friends had nicknamed him 'Teabag'.

"The cause of his death was what is called an Addison's disease crisis. Addison's disease is a rare but treatable disease."

A welfare officer at Ryan's school who was asked to look into his regular absences in the months leading up to his death noted that he looked "thin, grey and gaunt". A teacher said: "I noticed that his skin was dark. He looked Indian or Pakistani in race. There wasn't much of him."

Three days before his death his mother picked him up from school early because he was shaking, had vomited twice and complained of feeling ill.

At home his temperature changed from "very cold" to "burning", and his mother was so concerned that she slept with him in his bed. By the next day Ryan was delirious" and "talking rubbish".

Mrs Morse called the surgery and was told by Dr Thomas to "fetch him up" to see her, despite the fact he was "not able to carry his own weight". Later that day she made another phone call and spoke to Dr Rudling, who "also ignored" signs that Ryan was dying.

Dr Thomas later told an investigator from the Aneurin Bevan health board: "At no point did the mother ever ask me to visit him. But she said if he needed to be seen then she wouldn't be able to bring him in because he felt too ill."

Cardiff crown court heard that Dr Rudling later made false entries into Ryan's records two days after the boy's death. She allegedly made the notes look like they had been entered on the day his mother rang in for a consultation.

She is also accused of incorrectly noting that his genitals had "changed colour" when his mother had specifically said they were "black" in colour.

The trial continues.

Ryan Morse's skin went yellow and he had lost weight

Lindsey Thomas left, and Joanne Rudling

D. Sheridan, *The Times*, 5 May 2016.

7.7.1 Primary hypoadrenalism

In primary hypoadrenalism, the adrenal glands themselves are damaged or destroyed. The main cause used to be tuberculosis which remains a problem in developing countries, but in developed countries it is autoimmune adrenalitis, in other words autoimmune attack on the adrenal glands (Nicolaides et al., 2017). It can also occur when antibodies block the binding of ACTH to its receptors, preventing a response to ACTH to release cortisol. Infectious fungal diseases, viral infections, tumours, adrenal haemorrhage and genetic defects are other causes.

In this condition, production of all three hormone groups listed above is affected.

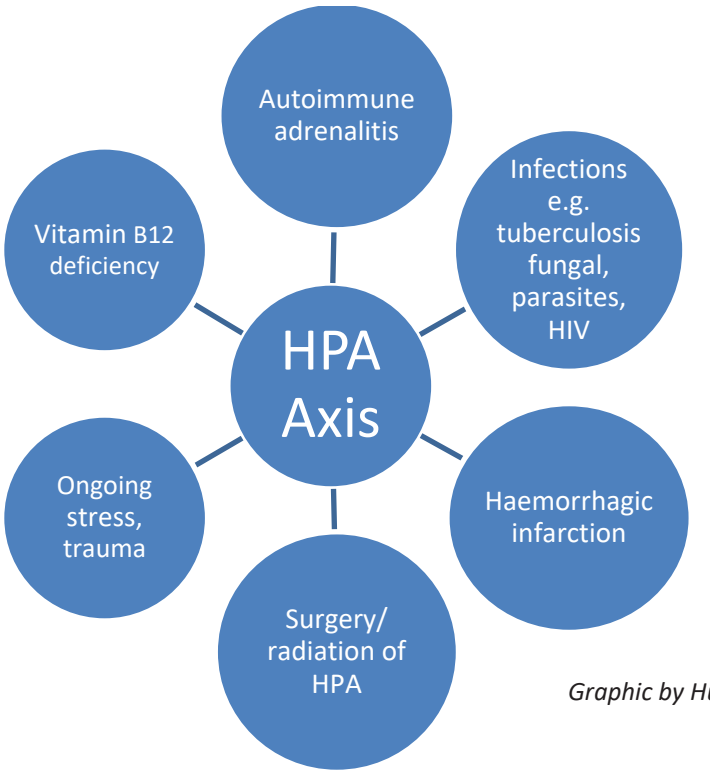
Autoimmune Addison's disease is chronic (i.e. long standing) and antibodies to the adrenal cortex may or may not be detected in a person's blood many years before damage to the adrenal cortex is apparent through low levels of cortisol. Chronic primary hypoadrenalism is held to be extremely rare, with a prevalence of 93-140 per million in the developed world (Arlt & Allolio, 2003). However, autoimmune adrenalitis appears to be increasing, implying that the prevalence of hypoadrenalism may also be rising (Laureti et al., 1999). In our Practice we encountered 15 cases of chronic hypoadrenalism (see, for example, Cases 7-3 and 7-5) as well as the case of a GP colleague who was the patient of another Practice (Case 7-4).

In general, at least 80% of both adrenal glands have to be damaged in order for deficiencies to become clinically evident. Signs and symptoms become critical when 90% of the adrenal cortex is destroyed. This is a problem for diagnosis as discussed below.

7.7.2 Secondary hypoadrenalism

Hypoadrenalism can also result from any disruption of the action of the pituitary gland which affects

Figure 7-5 Causes of hypoadrenalism: factors affecting HPA Axis



Graphic by Hugo Minney

secretion of the stimulating hormone ACTH as described in Figure 7-3. The most frequent causes of this condition are a pituitary tumour, surgery, or treatment with irradiation. In this case, the adrenal glands may still be intact. They are simply not receiving enough stimulation because the HPA axis is disrupted. Production of glucocorticoids will be affected but mineralocorticoid levels may be normal because mineralocorticoids are not controlled by the HPA axis. (They are under the control of the renin-angiotensin system – RAA.)

Secondary hypoadrenalism is more common than the primary form with an estimated prevalence of 150-280 per million (Arlt & Allolio, 2003). A frequent cause of secondary hypoadrenalism is therapeutic use of steroids for other conditions because this leads to atrophy of the pituitary corticotrophic cells. The dose given may be higher than the level the body normally produces, so if the patient takes corticosteroids for a long time, the adrenal glands produce less and may be slow to resume normal production when the prescription dose is stopped – which can cause adrenal insufficiency. For this reason, prescription doses should be reduced gradually. Conditions arising from this cause are usually reversible. In other cases, the cause may be autoimmune disorder (Kasperlik-Zaluska et al., 1998).

7.7.3 Tertiary hypoadrenalism

A third cause is any process that interferes with the hypothalamus and CRH production. As in secondary hypoadrenalism, the HPA axis is disrupted but the cause is different (Charmandari et al., 2014). The effect on hormone production will be the same as in secondary hypoadrenalism.

Among APS Type II patients, hypoadrenalism occurs with hypothyroidism in about 69% of patients, and with Type 1 diabetes in about 52% of cases (Sherman & Gagel, 2005). In established diabetes, a significant drop in the amount of insulin required to achieve the same glucose control may be a warning sign of developing hypoadrenalism.

Although the diagnosis is more common in people older than 30 years, children as young as five may also have symptoms which indicate Addison's disease.

7.7.4 Addisonian (adrenal) crisis

Untreated Addison's disease can be fatal and the deterioration can be rapid (see Plate 7.1). Adrenal crisis is likely to occur 6 - 8 times per 100 patient years, so a person with Addison's disease can expect four crises during their lifetime (Bancos et al., 2014).

Hypovolaemic shock, cardiac arrest, stroke, cerebral oedema or other circulatory complications can occur as a result of adrenal crisis. Complications may leave a patient with permanent disabilities, including permanent brain damage. Because of hyponatremia (low sodium, which affects the fluid balance in every part of the body), the doctor should recognise the condition and treat it correctly.

An acute exacerbation (adrenal crisis = patient collapse) should be considered an emergency and treated with IV hydrocortisone and a hospital admission. It can be brought on by a serious infection, acute stress, bilateral adrenal infarction or haemorrhage (Charmandari et al., 2014). In such cases, none or delayed treatment is more dangerous than treatment.

The symptoms of an Addisonian crisis include:

- Dehydration and/or severe vomiting and diarrhoea
- Stabbing pain in the abdomen, low back, or legs
- Low blood pressure (shock)
- Low blood sugar
- Loss of consciousness

Treatment includes:

- Rehydration by saline infusion at initial rates of 1 litre per hour (L/h), with continuous cardiac monitoring.
- Glucocorticoid replacement by bolus injections of 100 mg hydrocortisone followed by the administration of 100-200 mg hydrocortisone over 24 hours.
- Mineralocorticoid can be initiated once the daily hydrocortisone dose has been reduced to <50 mg, because at higher doses hydrocortisone provides sufficient stimulation of mineral corticoid receptors.

Life-saving treatment with steroids can only be given if the emergency medical team knows that the patient has hypoadrenalism. Addisonian crisis can affect a patient's thinking and even cause loss of consciousness, so all patients with adrenal insufficiency are advised to wear a medical alert bracelet or necklace that clearly states their diagnosis (Toft & Spinasanta, 2016). Patients should keep extra supplies of tablets at home or when on holiday as well as vials of hydrocortisone that they can inject.

Case 7-4 End-stage Addisonian Crisis presentation

In January 2013, Dr Jane Leigh joined the Shinwell Medical Practice GP Team of 4 GPs.

The Senior Partner (Dr Chandy) was concerned as she appeared quite ill and struggled to cope, asking for 20 minutes for each consultation and using a nebuliser (containing steroids) between consultations.

The Senior Partner decided to discuss her health issues with her. She told him that she had been ill for 17 years and had a diagnosis of ME/CFS, and that the immunology clinic at the teaching hospital had been searching for a viral cause (Epstein-Barr virus) for at least 10 years, without finding anything.

Her symptoms were classic symptoms of Addison's disease (extreme fatigue, weight loss, breathlessness, dizziness, syncopal attacks, feeling extremely ill and no energy to get out of bed etc.). It appeared that her early morning cortisol level had not been tested. On prompting, the immunology clinic carried out a straightforward blood test to determine her early morning cortisol level.

The result was: Baseline cortisol (0 m)	 0 nmol/L

She was immediately referred to the endocrinologist. A diagnosis of primary hypoadrenalism was confirmed, and the endocrinologist commenced her on hydrocortisone: 10 mg (am) + 10 mg (midday) + 5 mg (5 pm).

Dr Chandy suggested that the initial dose was not high enough and in fact, two weeks later, she developed gastritis and vomiting. She then collapsed at home in the early hours of the morning. A 999 crew arrived, but they were unable to administer the Efcortisol injection (a form of hydrocortisone) without a protocol. Eventually, the patient was admitted as an emergency and received IV Efcortisol, fluids and electrolytes. She now takes a hydrocortisone dose tailored better to her physiological need. Following this treatment, her health improved dramatically.

The "window of opportunity" to diagnose promptly and initiate appropriate replacement was 17 years previously. During this critical 17-year period she and her family undoubtedly suffered intense physical and psychological trauma from the ups and downs of her condition. The current guidelines are preventing Doctors (GPs and Consultants) from early diagnosis and treatment of this deadly condition; better guidelines would save many precious lives (Wass, 2012, p. 5063) – see also newspaper report above (Figure 7-4 and Sands (2017); Wass (2012)).

7.7.5 Diagnosing Addison's disease

The progression of Addison's disease is often gradual and may not be detected until an illness or other stress precipitates an adrenal crisis. It can progress undetected to the critical or emergency stage which requires immediate hospital admission. Long-term hypoadrenalism, if left uncorrected, could be fatal.

The main presenting symptoms of all forms of hypoadrenalism (fatigue, anorexia, weight loss) are non-specific and could be the result of any number of different causes; thus, there is a risk that diagnosis may be delayed. The principal symptom is overwhelming exhaustion, which is a result of low cortisol. When three or more of the following symptoms are present in the same patient, hypoadrenalism should be considered as part of the differential diagnosis:

- Feels faint, dizzy, headache
- Weakness, fatigue
- Anorexia, weight loss
- Abdominal pain, salt craving
- Loss of muscle mass
- Breathlessness

Note: Many of the signs overlap with those of Type 1 diabetes (also an autoimmune condition); however, in Addison's disease you would expect blood glucose to be normal or even low. Fatigue, sleepiness, thirst, and unexplained weight loss occur in both conditions.

As a person with hypoadrenalism does not have enough cortisol circulating during waking hours, they feel very tired throughout the day and particularly immediately after waking.

Other symptoms are hypotension, electrolyte imbalances such as hyponatremia (low sodium), hyperkalemia (high potassium), or metabolic acidosis, hyperpigmentation (dark skin patches – in primary adrenalism only), autoimmune manifestations (vitiligo – white skin patches), decreased axillary and pubic hair, and loss of libido and amenorrhea in women. However, in secondary hypoadrenalism there is no hyperpigmentation of the skin, because the secretion of ACTH is not increased. Also, since the production of mineralocorticoids is mostly intact, dehydration and hyperkalemia are not present, and hypotension is less prominent (Charmandari et al., 2014).

Besides tiredness and the symptoms listed above, there are many other symptoms to help a physician diagnose hypoadrenalism:

- Joint and muscle pain/weakness;

- Increased pigmentation of the skin – due to raised ACTH level (only present in primary hypoadrenalism – not present in secondary/tertiary hypoadrenalism);
- Depression;
- Decrease in axillary and pubic hair – common in women;
- Neuropathy, myopathy;
- Unsteadiness/falls;
- Postural hypotension (low blood pressure on standing up – mainly present in primary hypoadrenalism);
- Impotence and amenorrhoea;
- Hypoglycaemia – reduced opposition to insulin action.

Note: Blood pressure control is abnormal in severe cortisol deficiency (prone to postural hypotension). Very low blood pressure is a sign that the patient is in immediate danger of collapse. Patients with a severe deficiency of cortisol and the ***related hormone aldosterone*** *often have a low sodium level and increased potassium level.*

7.7.6 Current diagnostic guidelines inadequate

From our patient experience, we believe that the current guidelines to diagnose hypoadrenalism are unsafe and damaging to the patient: they result in either a delayed diagnosis, or an end-stage diagnosis when it is too late to treat (Wass, 2012). Others have also found that delay in diagnosing is a "frequent cause of adrenal crisis" (Papierska & Rabijewski, 2013). We recommend following the Protocol for diagnosing hypoadrenalism included at the end of this book.

There are a number of diagnostic tests but none are completely reliable for reasons explained below. For example, the commonly used high dose Synachten Stimulation Test (SST), in which 250 mcg of ACTH is injected to test for adrenal response, is only reliable when 95% to 100% of both adrenal glands are destroyed. This is because such a high dose is likely to produce a reaction from the adrenal glands even if they are severely impaired. Mild secondary adrenal insufficiency can pass the test showing an intact HPA axis, and conversely healthy individuals might fail any single test by a small margin. "Thus, clinical judgment remains important. Persisting symptoms such as fatigue, myalgia, or reduced vitality should lead to reassessment" (Arlt & Allolio, 2003, p. 1887), p. 1887). There are cases of suboptimal responses to high dose SST being reported as normal and therefore no replacement therapy considered. There are also cases where replacement therapy is withdrawn from hypoadrenal patients with suboptimal responses to high dose SST who have been clinically and physiologically benefiting from the therapy.

Levels of cortisol and ACTH in healthy individuals and patients suffering from hypoadrenalism are given in Table 7-4.

7.7.7 Some questions for the clinician to ask

- Take blood pressure sitting and standing. If the blood pressure drop is greater than 20 points, diagnose postural hypotension.
- Ask the patient if they frequently drop keys, struggle to climb stairs or to get up from a sitting or squatting position.

- Check oral mucosa pigmentation and skin where clothes rub; for hyperpigmentation: this may be a soft muddy colour or darker, depending on patient's natural skin colour. If present, this can indicate high ACTH.
- Measure electrolytes (low sodium (Na), high potassium (K)), blood glucose, 9am cortisol (diagnosis highly likely if cortisol <100 nmol/L, and although unlikely if cortisol >400 nmol/L it should not be excluded if the patient is acutely unwell).

7.7.8 Quick patient questionnaire – hypoadrenalism

This questionnaire [which is part of our **Protocol for Hypoadrenalism** – see Appendix 2] should be completed by the patient. It is sometimes helpful if they circle the actual symptom experienced. Few patients report the full complement; some may also report psychoses.

Box 7-2 Hypoadrenalism questionnaire

Instruction to the patient: *Please grade these symptoms 1-10 and circle most relevant symptoms. 1 indicates that this symptom is mild and infrequent. 10 indicates the patient has it all the time and it is severe and debilitating. A score of 5 indicates that the patient has the symptom and it affects their daily life to a moderate extent.*

Symptom	score
Joint and muscle pain/weakness	
Increased pigmentation of the skin – due to raised ACTH level (not in all cases); pigmentation may be accompanied by vitiligo. Occasionally (in children) the opposite – alabaster-like pallor	
Intermittent abdominal pain and salt craving	
Vague stomach ache or other gut symptoms, diarrhoea and nausea	
Experiences weakness, fatigue, anorexia and weight loss	
Feels faint, dizzy and has headache	
Signs & Symptoms usually subtle	
Depression/anger/difficulty concentrating	
Decrease in axillary and pubic hair – common in women; alopecia	
Loss of muscle mass	
Neuropathy, myopathy	
Dizziness, unsteadiness, falls, syncope	
Breathlessness, difficulty with speech, chest pain	
Postural hypotension, hyponatremia (low sodium)	
Impotence and amenorrhoea	
Hypoglycaemia	

Table 7-2 Blood levels of cortisol and ACTH

	ACTH	CBG Cortisol (Corticosteroid-binding Globulin [attached] cortisol)	Serum Free Cortisol (SFC)*
Healthy subject, fasting levels 8am-9am	30-60 ng/L	550-800 nmol/L	20% of CBG-C
Healthy subject, midnight levels	<10 ng/L	<100 nmol/L	20% of CBG-C
Primary adrenal insufficiency, fasting 8am-9am	>30 ng/L	<275 nmol/L, signs and symptoms present	Variable
Secondary adrenal insufficiency, fasting 8am-9am	<20 ng/L	<275 nmol/L, signs and symptoms present	Variable

Note: for cortisol levels some sources use µg/dL. The conversion factor is 27.6 (i.e. 10 µg/dL = 276 nmol/L). SFC refers to cortisol available to be used by cells

Compiled with reference to: Schlaghecke et al. (1992), Debono et al. (2009), Erturk et al. (1998), Oster et al. (2017), BMJ Best Practice 'Adrenal Suppression Investigations' (2018b) and 'Addison's disease: Investigations' (2018a). Healthy ACTH levels from Oster et al. (2017).

7.7.9 Confirming the diagnosis

Typically, three or more symptoms would indicate that hypoadrenalism should be considered. Before making a provisional diagnosis of hypoadrenalism, exclude all other possible diagnoses with appropriate blood test and investigations as clinically indicated.

When patients present with mild to moderate symptoms, the GP should order tests for: early morning fasting cortisol levels (8am – 9am) along with Full Blood Count (FBC), vitamin B12, folic acid, ferritin, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), parathyroid hormone, vitamin D, urea and electrolytes (U&Es), liver function, blood glucose etc. in order to differentially or concurrently diagnose ME, CFS, FM, MS-like presentation, depression, psychosis, vitamin B12 deficiency, myxoedema and so on.

The following table may be useful in making a diagnosis.

Table 7-3 Hypoadrenalism: Stages of disease progression

	Stage 1 Preclinical	Stage 2 Preclinical	Stage 3 Subtle	Stage 4 Clinically significant	Stage 5 Clinically critical	Stage 6 Clinical emergency
Signs and Symptoms	Mild	Mild to Moderate	Moderate	Significant	Critical	Emergency (adrenal crisis)
Early morning (fasting) cortisol	400-500 nmol/L	300-400 nmol/L	150-300 nmol/L	50-150 nmol/L	25-50 nmol/L	0-25 nmol/L

7.7.10 Tests to determine hypoadrenalism

7.7.10.1 Short Synacthen Test (SST)

The term "Synacthen" is an abbreviation of Synthetic ACTH Enhancement. In this test, a burst of artificial ACTH (cosyntropin) is given. Then blood samples of cortisol are taken at intervals (usually 0 mins, 30 mins, 60 mins after the ACTH administration) to test the response of the adrenal cortex and its ability to produce cortisol on stimulation. Where adrenal insufficiency is suspected, this test will distinguish between primary adrenal insufficiency (adrenal gland unable to produce cortisol in spite of stimulation), versus secondary adrenal insufficiency (adrenal gland functions as normal, but there is no ACTH to stimulate it until the SST is given).

We believe there are some problems with this test as routinely administered. The first derives from the size of the dose. SST provides a burst of 250 mcg of artificial ACTH (for a 65 kg person, with approximately 5 litres of blood, this is 50 mcg/L, or 50,000 ng/L). This is about 1,000 times as much as the expected concentration of natural ACTH at its peak (ACTH varies between 50 ng/L and 5 ng/L over the circadian rhythm, although it is delivered in a series of bursts (Oster et al., 2017)). This huge dose is likely to stimulate the adrenal cortex to produce some cortisol even if only 5% of the adrenal cortex remains (i.e. 95% is damaged and unable to function) which can lead to "falsely reassuring results" ("false negatives") (Abdu et al., 1999; Ferrante et al., 2012), whereas physiological doses of ACTH would not produce sufficient cortisol from such a small amount of remaining adrenal cortex.

However, ACTH does not affect only the adrenal cortex. It is contraindicated in some circumstances: a 250 mcg dose of cosyntropin can cause collapse in patients with allergies (Datapharm, 2017; Juno Pharmaceuticals, 2015), which is a risk because of the high dose being used for the standard SST.

7.7.10.2 Low-dose SST to detect partial hypoadrenalism

This test has the advantage that it can detect partial adrenal insufficiency that may be missed by the standard high-dose test. It is also preferred in patients with secondary or tertiary adrenal insufficiency, and is safer, for the reasons described above.

A low dose (500 nanograms – 1,000 ng (= 0.5-1 mcg) of ACTH – only slightly more than the 0.16-0.726 mcg that the pituitary naturally produces) is administered as an intravenous bolus. We believe that this test provides a more sensitive index of adreno-cortical responsiveness, because it results in physiological (appropriate to healthy or normal functioning) plasma ACTH concentration, i.e. the amount that the pituitary would normally produce when stimulated The low dose SST can be carried out in a primary care or community setting since it does not cause shock. The test should be carried out at 14.00 h, when natural ACTH production is low. A value of 500 nmol/L or more at any time during the test indicates normal adrenal function (Arlt & Allolio, 2003).

Note that these tests measure standard serum cortisol levels (not serum free cortisol). Since more than 80-90% of cortisol is bound to liver protein (Cortisol Bound Globulin (CBG)), serum free cortisol (SFC) is technically difficult to measure. So far there are no "gold standard" tests to measure unbound free/active cortisol.

The amounts of ACTH and cortisol in the blood naturally vary so a single random sample is not enough. Three or more weekly low or subnormal morning cortisol levels are clinically significant and should be clinically assessed and appropriate action taken.

7.7.10.3 Insulin tolerance test

This test, in which insulin is injected into a patient's vein, is an alternative for determining secondary hypoadrenalism. It helps to assess how well the HPA axis is functioning. This test can be dangerous. It is a powerful stressor and for this reason is contraindicated in patients over 60 years old, suffering from conditions such as ischaemic heart disease, seizures or cardiovascular disease, panhypopituitarism and severe hypoadrenalism. If the patient is taking hydrocortisone this should be discontinued for 24 hours before the test. It should also not be performed on children outside a specialist clinic.

7.7.10.4 MetyraponeTest

This test is used to detect secondary adrenal insufficiency. Metyrapone, which inhibits the conversion of 11-deosycortisol to cortisol, is administered overnight. In a healthy person, serum 11-deoxycortisol will increase as the HPA axis responds to the lack of cortisol. If the HPA axis is impaired, serum 11-deoxycortisol will not be more than 230 nmol/L at 8am (Arlt & Allolio, 2003, p. 1887).

7.7.11 Assessing cortisol levels

In a healthy person, cortisol is highest (550-750 nmol/L) in the morning within 30 minutes of waking up. Through the day, the level of cortisol is carefully regulated by the HPA axis: at midday it is around half the morning level, and by evening it will be 100-200 nmol/L to prepare the person for sleep.

An 8-9am cortisol level of less than <200 nmol/L is highly abnormal and strongly suggests a diagnosis of adrenal insufficiency. A cortisol level below <300 nmol/L (8-9 am fasting) should be cause for concern and anything below 400 nmol/L should be followed up. During acute illness, a cortisol level of less than < 500 nmol/L may be consistent with hypoadrenalism since the body would normally respond to such stress by producing more cortisol. Levels of 550 nmol/L or above exclude the diagnosis.

In primary hypoadrenalism, a patient's ACTH level is usually greater than 80 ng/L. But if the patient is suffering from pituitary disease or steroid suppression of the action of the hypothalamus, the ACTH level is undetectable (less than 10 ng/L). When early morning cortisol is <270 nmol/L or cortisol, ACTH and DHEAS levels are subnormal, hydrocortisone therapy is continued.

If three or more 8-9am weekly total cortisol CBG (cortisol binding globulin) levels are consistently reported as <270 /<300 nmols/L and the patient is presenting with moderate-to-severe classic signs and symptoms of hypoadrenalism and other autoimmune conditions, a three-month therapeutic trial of physiological replacement doses of hydrocortisone (total dosing of 15-25 mg/day) is commenced. This is followed by monthly clinical review and adjustment of the hydrocortisone dosing in accordance with a *Hydrocortisone Day Curve (HCDC)* carried out in the Primary Care setting (see the **Protocol for diagnosing hypoadrenalism (Appendix 2)**).

Prompt clinical diagnosis and physiological replacement can reverse the progression of the condition at early stages i.e. 2, 3 & 4 (Table 7-3) of presentation. Thus, possible regeneration of the adrenal glands can be achieved by this early intervention.

7.7.12 Limitations of the tests: high CBG levels

As with all laboratory tests, there are limitations. One of these is that the SST tests do not take into consideration a patient's level of CBG which affects their cortisol levels. Researchers have shown that: "CBG varies significantly within and between individuals. This is accompanied by changes in serum total cortisol large enough to affect the outcome of an SST and, by implication, other tests of the HPA axis" (Dhillo et al., 2002). Misleading results from the SST (and also the Insulin Tolerance Test) have life-threatening consequences so it is extremely important to interpret the results with reference to the individual's CBG levels.

Considerable work has been done on this subject by Dr Mike Welch who has shown that in a small proportion of patients who clinically manifest the signs and symptoms of adrenal insufficiency, the SST as currently performed fails to support the diagnosis of Addison's disease. Instead it may show either an unexpected normal result, or a sub-optimal response to ACTH from, often, a normal baseline. Furthermore, results may vary on subsequent repeated SSTs from previous investigations.

A modification to the SST whereby free cortisol in plasma is the required measurement, together with an assay of CBG, may be required to enable the clinician to establish a diagnosis of atypical, or high CBG, Addison's disease.

Current methodology for the assay of free cortisol in plasma is not yet established as an accredited technique. This requires urgent attention (Welch, 2006).

7.7.13 Sound and safe approach

The above simple but sound and safe approach to diagnosis that we have developed enables the physician to arrive at a clinically robust diagnosis of hypoadrenalism. A safe and side-effect free, medium-to-long-term treatment can then be instituted. The advantages are:

- Optimum physiological dosing prevents any further destruction of the remaining functioning cortical cells;
- Regular monitoring with an HCDC reassures the patient and enables the clinician to fine-tune the cortisol dosing accordingly;
- Normal cortisol circadian adrenal function is restored which allows the person to live a normal life;
- If the "window of opportunity" has not been missed, partial or total regeneration of the adrenal gland can take place once the adrenal cortex is given a rest;
- If and when the adrenal cortex regenerates, then replacement treatment is reduced, or even, in rare cases, withdrawn;
- Even when a hypoadrenal patient requires lifelong replacement of oral steroids, because the dose is physiological, there will not be any adverse effects, as one might expect when long-term pharmacological doses of steroids are administered in various other clinical situations.

7.7.14 Effect of hypoadrenalism on fertility and the female sexual cycle

Women with adrenal insufficiency often suffer from androgen deficiency which can contribute to low energy levels and cause loss of libido. Dehydroepiandrosterone (DHEA) supplementation of 25-50 mg (total daily dose) may be needed. Female fertility is broadly controlled by a number of hormones, including oestrogen and progesterone, which maintain the monthly cycle.

The hypothalamus and pituitary are closely involved in this monthly cycle, and the hypothalamus releases a hormone to make a follicle release an egg, when oestrogen levels in the blood are highest.

This cycle is particularly sensitive to vitamin B12 deficiency, not only because of the large number of hormones involved but also because of the sensitivity of the hypothalamus to oestrogen, before an egg can be released.

In our experience, a great many women who have had heavy menstrual bleeding (HMB or menorrhagia) have been completely cured, and their ability to conceive and have children has been restored, through vitamin B12-replacement therapy (see Chapter 5).

Case 7-5 Classic case of APS: Angela Abraham

From age 14 onwards, Angela suffered from dizziness, fainting, feeling cold all the time, nausea, muscle cramps, hair loss, IBS and stomach pain, palpitations, thirst, panic attacks and loss of concentration. She has a family history of autoimmune problems and vitamin B12 deficiency.

She had many previous diagnoses, including the glandular disorder Polycystic Ovary Syndrome (PCOS), vitamin D deficiency, depression, comfort eating, obesity, ME/CFS-, FM-like presentations.

In September 2000, we diagnosed her with vitamin B12 deficiency and began replacement therapy. Some of her symptoms improved. In 2006 she suffered from menorraghia with chronic pelvic pain and underwent an abdominal hysterectomy.

At this time, due to the PCT embargo (see Introduction) we were not able to administer B12 therapy and her symptoms re-emerged. Her morning cortisol level was found to be low at 212 nmol/L so we referred her to an endocrinologist who arranged a high-dose SST. This showed a sub-optimal response but a further test two months later showed slightly higher levels; the first test results were therefore attributed to long-term use of steroid inhalers and she was discharged by the endocrinologist in May 2012.

We were able to resume vitamin B12 therapy after February 2011 when the PCT embargo was lifted but by then the "window of opportunity" to prevent further deterioration had been missed. Her health symptoms worsened and in 2013 we again referred her to an endocrinologist with comprehensive clinical supporting evidence to suggest hypoadrenalism and possible APS. A further SST confirmed extremely low levels of cortisol and a low level of ACTH, giving a diagnosis of secondary hypoadrenalism. Once the diagnosis was confirmed, Angela was given the correct cortisol supplementation and her condition improved. With accompanying vitamin B12 injections

her overall condition improved dramatically. Follow-up management included routinely conducting HCDCs in the primary care setting.

Despite being given multiple high-dose SSTs, Angela was not diagnosed as suffering from Addison's disease until she was almost at crisis point. This illustrates that the adrenal cortex can continue to produce cortisol when stimulated by 250 mcg Synacthen, until it is completely burnt out (see 26/07/2013 line in the chart below).

Chart 7-2 Results of multiple SSTs on a single patient

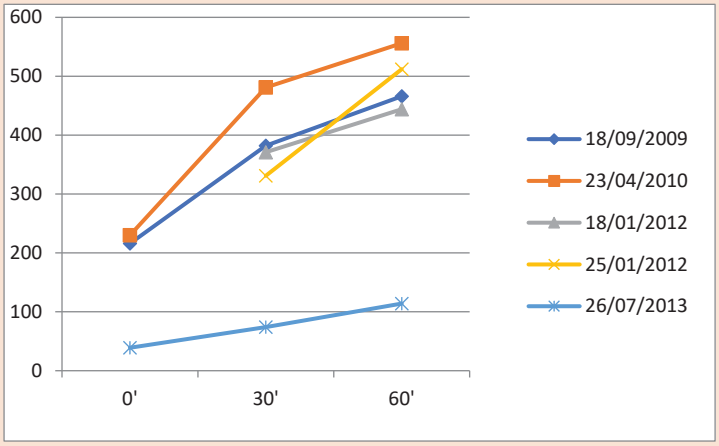


Table 7-4 Angela Abraham – timeline summary

Other conditions	B12 deficiency, PCOS, vitamin D deficiency, depression, comfort eating (sweet craving), obesity, ME, CFS, FM-like presentation											
Signs & Symptoms	Age 14 onwards – Dizziness, fainting, tiredness, weakness, feeling cold all the time, nauseous, muscle cramps, hair loss, IBS, stomach pain, palpitations, thirsty, headache, depression, panic attacks, loss of concentration, Mind switches off. (signs & symptoms) +++++											
Date **Hospital / GP**	10/06/09 GP	06/08/09 GP	18/09/09 Hospital 1	23/04/10 Hospital 1	15/12/11 GP	18/01/12 Hospital 2	25/01/12 Hospital 2	24/08/12	10/12/12 GP	11/02/13 GP	04/06/13 Hospital 3	26/07/13 Hospital 3
8-9am Cortisol **Signs & Symptoms severity marked by * (1-5)**	212 nmol/L fasting S&S ***** Referred to Hospital 1 by Dr Chandy	146 nmol/L fasting S&S ***** Awaiting Hospital 1 appointment	SST 250 mcg ACTH test 0' 216 30' 382 60' 466 S&S ***** ??ACTH level (not reported)	SST 0' 230 30' 481 60' 556 S&S ***** ??ACTH level (not carried out)	209 nmol/L fasting S&S ***** 28/12/11 Referred to Hospital 2	SST 0' * 30' 371 60' 444 S&S ***** Baseline cortisol missing, ACTH 37 ng/L	SST 0' * 30' 331 60' 512 S&S ***** Baseline cortisol & ACTH not reported	139 nmol/L fasting	263 nmol/L fasting S&S *****	303 nmol/L fasting S&S ***** 24/04/13 – Referred to Hospital 3 by Dr Chandy	**73** nmol/L fasting S&S ***** Clear Adrenal Insufficiency although not diagnosed by hospital	**0' 39** 30' 74 60' 114 S&S ***** Adrenal Insufficiency confirmed
Treatment or time-specific medication	No steroids	No steroids	No steroids	No steroids	No steroids	No steroids	No steroids		Steroid inhalers	Steroid inhalers	Hydrocortisone 10mg – AM 10mg – 12 Mid-Day SPR – Hospital 3	Hydro-cortisone stopped for 2 days.
Comments/observations	GP suspects Hypo-adrenalism having treated/excluded other conditions B12 248 ng/L	GP continues to be concerned	RVI **'?Early Addison's disease, Impaired response will take this further'**	RVI **'Could still be early Addison's. Long Synacthen Test Proposed'** No appt received by patient, nor a discharge letter to GP		HGH Confirmed	HGH confirmed **'SST Normal, No follow up necessary, Discharged'**		Fatigue, breathlessness. S+S worsening. On steroid inhalers.	Fatigue, breathlessness.	SPR from Hospital 3 telephoned Dr Chandy: **Urgent, Commence Hydrocortisone** **14.06.13** Height: 5f 3" Weight: 19st 10lb BMI: 48.83kg/m2	
Medication (choices available)	Terbutaline Inhaler (Inh), Symbicort 200/6 Inh, Simvastatin 20mg, Sertraline 100mg, Naproxen 250mg, Mebeverine 135mg, Metformin 500mg (PCOS), Lansoprazole 30mg, GTN Spray, Hydrocortisone (15mg am & 10mg midday, 5mg pm), Furosemide 40mg, Colecalciferol 800 units as needed, Aspirin 75mg, Co-codamol 30/50mg											

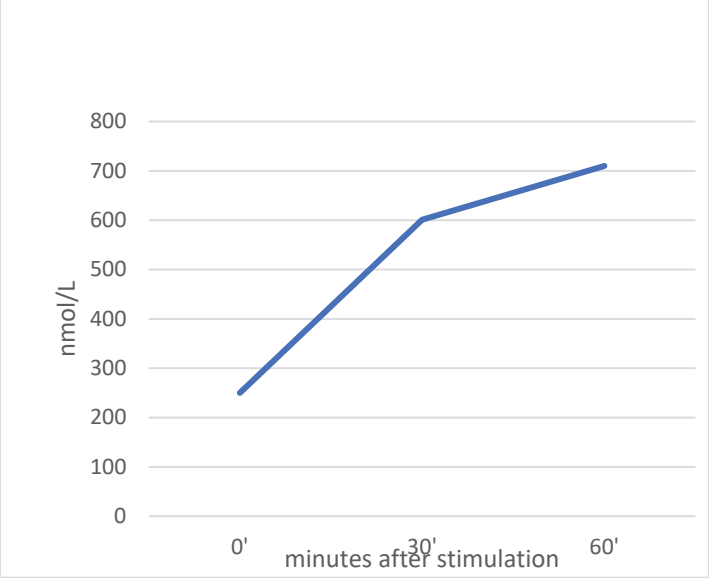
Case 7-6 Undiagnosed APS with hypoadrenalism leading to irreversible damage: Leanne Walker (née Chandy)

Leanne suffered from her early 20s with tiredness, dizziness, muscle weakness, weak grip, feeling cold, crampy pain, breathlessness, difficulty with speech, unexplained loss of weight, absent reflexes, many other gastrointestinal symptoms, and memory loss. Over the years she had received a number of diagnoses, including Polycystic Ovary Syndrome (PCOS), hirsutism, oligomenorrhagia, vitamin D deficiency, postpartum haemorrhage/hypovolaemic shock.

In 2002, an endocrinologist at a south of England hospital clinically suspected hypoadrenalism but no action was taken. In 2008, an endocrinologist at another hospital arranged a SST because of her signs and symptoms and endocrine disturbances. In January 2008, she was given a high-dose SST which showed an extremely low ACTH level of 7 ng/L at 9 am, with a low cortisol level of 70 nmol/L, results which should have raised suspicions. But as the SST showed that her adrenal cortex was able to manufacture cortisol (when stimulated to this high degree), primary hypoadrenalism was excluded. There was no follow-up of the ACTH result to investigate secondary hypoadrenalism and no steroids were given.

In our view, the tests showed that two glands (the pituitary and adrenals) were malfunctioning. Together with other glandular problems (i.e. PCOS), this should have raised suspicions of hypoadrenalism.

Chart 7-3 Short Synacthen Test - hypoadrenal



In March 2011, two GPs made home visits and observed: fatigue and lethargy; symptoms worsening; leg pains and cramps; muscle loss; difficulty standing up from sitting; reduced power in all limbs; inability to stand on left foot; speech, swallowing and breathing difficulties. Given the severity of deterioration, she was admitted to hospital.

She was given further early morning cortisol tests which showed low cortisol levels (194 nmol/L and 252 nmol/L) but the endocrinologist concluded that her symptoms were "psychologically mediated" and did not prescribe any medication.

She did her own research and decided to self medicate with hydrocortisone she purchased from the internet, 25 mg/day. Once this treatment was started, the patient began to recover. In 2013 she was officially diagnosed by a different hospital as suffering from secondary hypoadrenalism.

Higher cortisol levels from treatment were reflected in that she was not as tired, and was more able to spend time with, and enjoy her family. She was also diagnosed with subtle vitamin B12 deficiency and given vitamin B12 therapy.

The patient still suffers from weight loss, probably because of the delay in diagnosis being made. However, she is much better.

The points to note from this case are

- The patient's am/pm fasting cortisol levels were subnormal from January 2008 (70 nmol/L at 4 pm), and were dropping steadily from 56 nmol/L to 17 nmol/L from March to May 2013 despite physiological doses of steroids. This should have warranted further investigation.
- The two ACTH levels measured (7 ng/L in 2002 and 12 ng/L in November 2013) were indicative of near-adrenal crisis but no action was taken.
- The undiagnosed secondary hypoadrenalism had caused disuse atrophy of the adrenal glands, leading to progressive primary adreno-cortico failure despite steroids being administered since August 2011. The result was partial primary and partial secondary hypoadrenalism.

The "window of opportunity" at the first investigation in 2002 to preserve the patient's optimal health and wellbeing was lost forever, resulting in irreversible damage and great distress to her and her family.

Chart 7-4 Early morning cortisol with hypoadrenalism

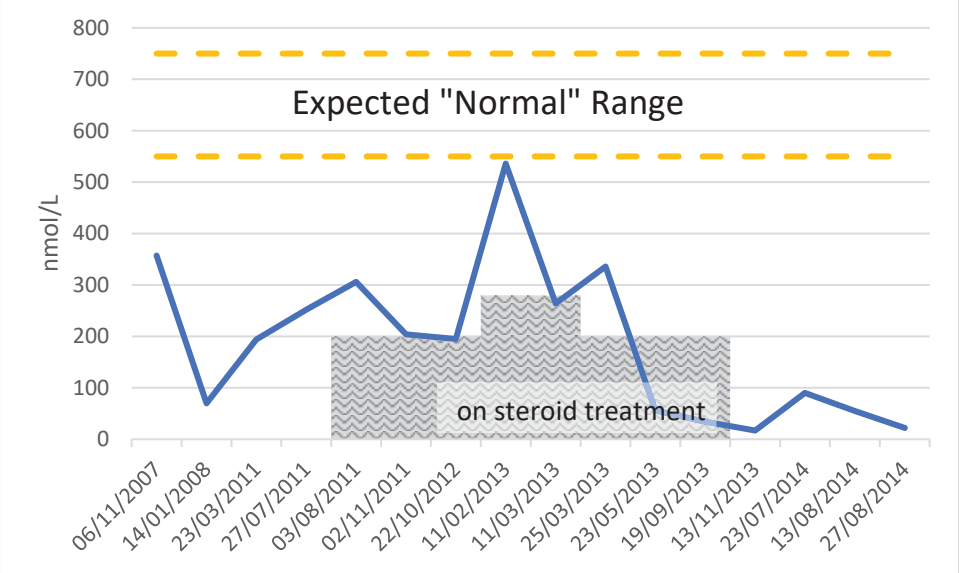


Table 7-5 Leanne Walker (née Chandy) – timeline summary

Other conditions	2002 PCOS, hirsutism, oligomenorrhagia, vitamin D deficiency; 2009 Post-partum haemorrhage/hypovolaemic shock, vitamin B12 deficiency								
Signs & Symptoms	Tiredness, feels faint, dizziness, muscle wasting, weak grip, feeling cold, crampy pain, breathlessness, weakness, extreme fatigue, chest pain, difficulty with speech, loss of weight (8st7lb to 7st), absent reflexes, loss of power both legs, unsteady gait, falling back, vague stomach ache, other GI symptoms and memory loss								
Date	16/11/07 Hospital 4	14/01/08 Hospital 1	23/03/11 Hospital 1	3/08/11	22/10/12	6/11/12-7/10/13 Hospital 3	25/10/13 (Hospital 4 inpatient 13/11 – 15/11)	21/7/14 GP	27/8/14 GP
Cortisol (nmol/L)	357 fasting (hypoadrenalism suspected)	70 nmol/L fasting cortisol ACTH 7 ng/L	194 fasting	252 fasting (on HC)	195 fasting (on HC)	Fasting Cortisol and fasting ACTH not tested 9/3/13 SHBG 46.5; TSH 0.42; T3 4.0, T4 15.6; Na 142	Cortisol 17 fasting (8:30am); 472 (11:07am); 784 (4:08pm) ACTH 12 (8:30am); <5 (2pm)	Cortisol 90 (9:27am) ACTH <5	13/8/14 cortisol day curve: 55 (8:46); 658 (11:15); 788 (13:12); 546 (14:50); 259
Medication Use				Self medicating 25mg hydrocortisone daily	Self medicating		27.5mg hydrocortisone	20mg plenadren	20mg plenadren
Other observations	5/12/01 Testosterone 3.6 nmol/L - excess	Vit D 20 nmol/L, Recom-mendation "it would be worth excluding hypo-adrenalism"	19/3/11 EMG nerve conduction normal Vit D 94.9 nmol/L Na 133 BP 90/48	19/8/11 Hospital 1: "symptoms psychologically mediated. Do not delay her appropriate referral to psychology, physiotherapy and CFS service"	31/3/12 Echo – normal LV function 23/3/12 Muscle biopsy – myopathic changes		Confirm secondary adrenal insufficiency Other pituitary dysfunction excluded Myasthenia Gravis excluded	Ferritin 46 ng/L (low), Hb 112 g/L (low)	Consider hospital admission for adrenal insufficiency

In both patients (Case 7-5 and Case 7-6), we developed the spreadsheet format for presenting the data so that a doctor could see at a glance the patterns evolving. This enabled us to recognise the same symptoms across multiple patients, and begin to understand that the likely cause was treatable rather than untreatable. It led us to recognise the link between these endocrine conditions, autoimmune disease, and vitamin B12 deficiency, and so identify that vitamin B12-replacement therapy (B12 injections) could help many of these patients previously diagnosed as incurable.

7.7.15 Management and treatment of hypoadrenalism

Identifying the cause of hypoadrenalism (whether primary, secondary or tertiary) will determine the best course of treatment.

7.7.15.1 Importance of including vitamin B12-replacement therapy.

If the "window of opportunity" to correct the condition has not been missed, the use of optimum replacement therapy of vitamin B12 and other nutritional support to restore the adrenal cortex will reduce or remove all symptoms and debilitating signs and the patient will regain their former health. In many cases, supplementation with oral cortisol will allow the adrenal cortex to recover, although there are risks associated with this.

7.7.15.2 Chronic adrenal insufficiency

Glucocorticoid should be administered at a dose that replaces the physiological daily cortisol production. This is usually achieved by the oral administration of 15-25 mg of hydrocortisone in two-to-three divided doses. Doses are determined according to the severity of the condition. A typical hydrocortisone dose would be: 10 mg at 9:00am; 10 mg 12:00midday; 5 mg 5:00pm. Doses should be adjusted following the results of an HCDC and clinical evaluation.

Note that pregnancy may require an increase in hydrocortisone dose by 50% during the last trimester.

At least half of the daily dose should be taken in the morning. Long acting glucocorticoids such as dexamethasone are not preferred as they result in increased glucocorticoid exposure **(more so with dexamethasone, than prednisolone)** due to extended glucocorticoid receptor activation at times of physiologically low secretion (Charmandari et al., 2014).

Monitoring of glucocorticoid replacement is mainly based on the patient history and signs and symptoms suggestive of glucocorticoid over- or under-replacement. Plasma ACTH, 24-hour urinary-free cortisol, or serum cortisol day curves, reflect whether hydrocortisone has been taken or not but do not convey reliable information about replacement quality.

All patients with adrenal insufficiency need to be instructed about the requirement for stress-related glucocorticoid-dose adjustment. This generally means doubling the routine oral glucocorticoid dose in the case of intercurrent illness with fever, and bed rest. Daily IV injections of 100 mg of hydrocortisone may be needed in case of prolonged vomiting, surgery or trauma (Charmandari et al., 2014).

7.7.15.3 Mineralocorticoid replacement in primary hypoadrenalism

Patients suffering from primary hypoadrenalism will also need a daily dose of 100-150 mcg fludrocortisone. Adequacy of treatment can be evaluated by measuring the patient's blood pressure sitting and standing.

7.7.15.4 Adrenal androgen replacement

This is an option in patients with lack of energy, despite optimised glucocorticoid and mineralocorticoid replacement. It may also be indicated in women with features of androgen deficiency, including loss of libido. Adrenal androgen replacement can be achieved by once-daily administration of 25-50 mg DHEA.

General advice to patients:

- Simplify your life
- Reduce the amount of carbohydrate in your diet
- Exercise moderately

Case 7-7 Rapid results from treatment – vitamin B12 deficiency and hypoadrenalism

This patient was diagnosed with vitamin B12 deficiency in another Practice in February 2011, with a blood B12 level of 176 ng/L; the Practice started her on three-monthly injections.

These did not resolve the problem, and by November 2011 her blood B12 had fallen to 132 ng/L. She was suffering fatigue, lack of energy, and joint pains.

Due to the illness, she had to move and registered at our Practice, where her vitamin B12 deficiency was re-checked during the Practice health check, since it was already recorded amongst her existing conditions.

At the Shinwell Medical Practice, daily vitamin B12 injections were prescribed and these resolved most of the problems. However, she still suffered from fatigue and lack of energy, and in May 2013 we took an early morning cortisol test and identified hypoadrenalism.

Physiological replacement of cortisol was prescribed (oral) mimicking the daily cycle, to facilitate her recovery. By August 2013 she had recovered to the extent that physiological replacement was no longer necessary.

7.7.15.5 Monitoring the glucocorticoid replacement

There are no easy ways to monitor the effectiveness of dosage so this must be based mainly on assessment of clinical signs and symptoms. "Thus, long-term management of patients with adrenal insufficiency remains a challenge, requiring an experienced specialist. However, all doctors should know how to diagnose and manage suspected chronic or acute adrenal failure" (Arlt & Allolio, 2003).

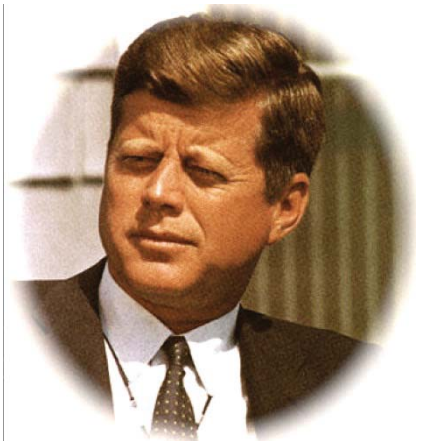
7.7.16 Cushing's Syndrome

Cushing's syndrome is a disorder which occurs when the body's tissues are exposed to high levels of cortisol for too long, for example by over-prescription of steroids for asthma, rheumatoid arthritis,

lupus, and other inflammatory diseases (NIDDK, 2018). Other people develop Cushing's syndrome because their bodies produce too much cortisol.

Cushing's syndrome has high morbidity or mortality, but it is less common now that doctors prescribe steroid hormones appropriately. If it is not caused by over-prescription of steroid hormones, it could be caused by high levels of ACTH which over-stimulate the adrenal cortex, or by damage to either pituitary or adrenal cortex.

Box 7-3 JFK and Addison's disease



The opening of the White House medical records of former US President John F. Kennedy in 2002 revealed that he had a complex medical history, including severe back pain (Pait & Dowdy, 2017) and glandular disorders from childhood which are now understood to have been Autoimmune Polyglandular Syndrome Type II. While in London in 1947, before he became President, he collapsed and was treated in St Thomas's Hospital, London, having been admitted with nausea, vomiting and hypertension. He was diagnosed as suffering from Addison's disease. The story given to the public, however, was that he had suffered a recurrence of malaria contracted in the Pacific during the Second World War. In the 1960s' presidential campaign, his supporters denied that he had Addison's disease, basing their interpretation on a narrow definition of Addison's disease as resulting only from tuberculosis which he did not have. The most common cause by then (and the cause of his condition), however, was autoimmune adrenalitis. Medical records and other documents also show that he suffered from hypothyroidism: these two glandular conditions point to the conclusion that he suffered from APS Type II. There was also evidence of a familial connection since his sister suffered from Addison's disease and his son had Graves' disease. He also had gastrointestinal symptoms which indicate other autoimmune conditions associated with APS. One of his physicians also said publicly that he was anaemic and was treated with vitamin B12, vitamin B1 and other B-complex vitamins. The White House records show that he was given vitamin B12 injections throughout his presidency. Recent interpretations suggest that he may have been suffering from pernicious anaemia (which is consistent with a diagnosis of APS Type II) but there is no definitive confirmation of this (Mandel, 2009).

7.8 SECTION 3: Other APS component illnesses

7.8.1 Underactive thyroid (myxoedema)

As described above, hypothyroidism (myxoedema) is frequently seen in APS. Underactive thyroid is thought to occur in a similar manner to adrenal insufficiency. It takes two forms depending on whether the thyroid gland itself is damaged (primary hypothyroidism) or is simply understimulated because of reduced TSH production by the pituitary gland (secondary hypothyroidism). Both hypo- and hyper-thyroidism may be caused by autoimmune disease. In hypothyroidism this is called Hashimoto's thyroiditis and in hyperthyroidism it is known as Graves' disease.

Primary hypothyroidism presents as elevated TSH; secondary hypothyroidism will have low TSH. Secondary hypothyroidism occurs alongside autoimmune Addison's disease in a large percentage of

patients. The patient and clinician should note that starting thyroxine replacement without treating the cortisol deficiency can exacerbate hypoadrenal symptoms and may precipitate adrenal crisis.

The thyroid gland produces thyroid hormones which influence the metabolic rate and protein synthesis, and have many other effects. They increase the strength of the heartbeat, the rate of breathing, intake and consumption of oxygen, and the activity of mitochondria. Combined, these factors increase blood flow and affect the body's temperature. They increase the growth rate of young people, and cells of the developing brain, and are particularly crucial for brain maturation during foetal development.

Appetite and the digestion and absorption of foods, including glucose, fats, and free fatty acids are all dependent on thyroid hormones. Thyroid hormones reduce cholesterol in the blood. They also play a role in maintaining normal sexual function, sleep, and thought patterns. Increased thyroid hormone levels are associated with increased speed of thought generation, but decreased focus. Sexual function, including libido and the maintenance of the normal menstrual cycle, are all influenced by thyroid hormones.

Patients present with trigger symptoms and family history of myxoedema. Other autoimmune conditions may be present. Blood tests should be ordered for TSH, T3, T4 and also tests to exclude other possible conditions. TSH is reported as high, T4 is low or subnormal and thyroid antibodies in most cases are absent. Diagnosis of myxoedema is made by the clinician and according to the severity, the levothyroxine dose prescribed is adjusted up or down at the recommended review dates. ***No secondary care dynamic tests are mandatory for the above diagnosis or monitoring of treatment.***

7.8.2 Diabetes mellitus

Diabetes is a disease that occurs when blood glucose, also called blood sugar, is too high because not enough insulin is being produced by the pancreas to manage sugar levels or because cells are resistant to the effects of insulin. Over time, having too much glucose in the blood can cause health problems, such as heart disease and stroke, nerve damage, poor blood flow in the feet, kidney disease and eye problems (NIDDK, 2016).

The cells in the body need sugar for energy. However, the times when cells need energy are often different from the times when there is sugar in the bloodstream (after a meal). Blood sugar after a meal needs to be stored in the liver or in longer-term storage; and sugar needs to be released from storage to reach the cells when they need energy. Insulin controls this. It stops the blood sugar level from getting too high (hyperglycaemia) or too low (hypoglycaemia). Blood sugar levels may fluctuate wildly with intake (e.g. in a meal), and the cells may not be able to absorb enough blood sugar to perform functions such as physical activity.

7.8.2.1 Type 1 Diabetes

People with Type 1 diabetes cannot make insulin (beta cells in the pancreas are damaged or destroyed by autoimmune attack). They typically need insulin injections to trigger the cells to absorb sugar from the blood, avoiding hyperglycaemia which can cause permanent damage to many body systems. Up to one-third of patients with Type 1 diabetes may develop APS (Van den Driessche et al., 2009).

Vitamin B12 deficiency due to pernicious anemia has been found to occur frequently among patients with Type 1 diabetes. Primary autoimmune hypothyroidism and coeliac disease are also frequently present in such patients, both of which affect vitamin B12 metabolism (Kibirige & Mwebaze, 2013).

7.8.2.2 Type 2 Diabetes

People with Type 2 diabetes have cells that are resistant to insulin, that is they do not respond (by absorbing blood sugar) to normal levels of insulin in the blood. Typically, they are treated with oral medications, along with diet and exercise. Diabetes is thought to be a progressive condition so it is assumed that the longer someone has Type 2 diabetes, the more likely they will require insulin injections to maintain blood sugar levels.

It is also well documented that vitamin B12 deficiency is prevalent among patients with diabetes mellitus who are taking the glucose-lowering medication metformin (Valdes-Ramos et al., 2015).

We have found that vitamin B12 therapy can help relieve symptoms of both types of diabetes if administered alongside the normal medication for diabetes. Pancreatic function appears to improve as evidenced by patients needing less insulin.

7.8.3 CFS/ME- and FM-like presentations

Conventional wisdom is that the cause of conditions labelled Chronic Fatigue Syndrome (CFS – also known as Myalgic Encephalomyelitis (ME)) and Fibromyalgia (FM) is not known. CFS may be triggered by "viral infections, such as glandular fever, bacterial infections, such as pneumonia, problems with the immune system, a hormone imbalance, mental health problems, such as stress, depression and emotional trauma" or have a genetic origin (NHS, 2017). These are conditions with a range of symptoms, including fatigue, sleep disturbances, muscle pain, cognitive dysfunction, gastrointestinal dysfunction, headaches and postexertional malaise.

However, one specialist traces the cause to HPA axis dysfunction (Holtorf, 2008). He also notes that patients suffering from these symptoms often have hypothyroidism (although it is not easily detected), and low growth hormone (again not detected by standard testing). They also have associated mitochondrial dysfunction, immune dysfunction and gastrointestinal dysfunction.

These observations confirm our experience that these conditions are also consequences of vitamin B12 deficiency plus a glandular disorder (itself caused by B12 deficiency either directly or indirectly). We are not the only medical professionals to have noticed the link with vitamin B12. Regland et al. also observed that vitamin B12 with folic acid proved helpful in providing "good and safe relief" to sufferers of these conditions (Regland et al., 2015).

With regard to treatment, Holtorf advises that physiologic doses of cortisol should be considered as part of a multisystem treatment protocol for CFS and FM, especially where there are signs or symptoms of adrenal dysfunction, low blood pressure and/or serum levels that are low or in the low-normal range (Holtorf, 2008).

7.8.4 Autoimmune skin conditions

7.8.4.1 Vitiligo

Vitiligo (white patches on the skin caused by lack of skin pigment) is often present in sufferers of autoimmune disease. In the 1970s, a researcher at the Royal Victoria Infirmary, Newcastle-on-Tyne,

reported that vitiligo had been found in association with several autoimmune diseases, including thyroid disease and Addison's disease. He concluded that "vitiligo is evidently another 'skin-marker of internal disease'" and that patients should therefore be monitored for the development of other autoimmune conditions (Dawber, 1970). Classical understanding is that there is no cure although symptoms may be alleviated (NHS, 2016e).

7.8.4.2 Alopecia

Alopecia areata (hair loss) is another autoimmune skin disease for which there is considered to be "no cure". In our experience, however, alopecia can be cured with vitamin B12 therapy. We had several patients suffering from this condition who were diagnosed as vitamin B12 deficient. Conventional treatment by a dermatologist had no impact, but within seven months of commencing intensive vitamin B12 treatment, the condition was completely cured.

7.8.4.3 Urticaria

Chronic idiopathic urticaria has also been found both to have a possible autoimmune origin and to be related to vitamin B12 deficiency. In 2004 Turkish researchers found vitamin B12 levels below the normal reference range in one-third of patients with this condition although none of the patients had developed clinical signs of vitamin B12 deficiency. They also found a higher frequency of antithyroid and anti–gastric parietal cell antibodies in the patients with low vitamin B12 levels, suggesting an "autoimmune etiology in B12 deficiency" (Mete et al., 2004).