

**From NZAN's Medical
Advisor,
Professor Ian Holdaway:

Contributions to NZAN
Newsletters, November
2002, to August 2004**

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1. Does Addison's contribute to anaemia?

2. Under what circumstances should people with Addison's disease also have their blood glucose checked?

Reminder: monitoring thyroid function

**In response to questions from
members:**

**1. HRT – what are the risks and
benefits for Addisonians?**

Question: "A member now in her early 50s with primary Addison's disease asks whether HRT is safe for her situation. She has taken HRT since early menopause in her late 30s. Her mother was diagnosed with breast cancer aged mid-50s."

Answer: Hormone replacement therapy (treating females with estrogen therapy during or following menopause, or after removal of the ovaries) has become a hot topic following announcement of the findings from the Women's Health Initiative study in the USA.

The issue is even more relevant for those with Addison's disease since there is sometimes an interaction between HRT and glucocorticoid treatment.

The WHI study found that there was the expected small increase in risk of developing breast cancer with HRT (this had been found previously in analysis of observational studies), and lowered risk of hip fracture (as also known from previous data).

However, the surprise finding of the study was that the risks of clotting in the veins, as well as heart attack (clotting in the coronary arteries) and stroke (clotting in the arteries in the brain), were all slightly but significantly increased in the group treated with HRT compared with controls given dummy tablets. The previous observational studies had suggested there might be protection against stroke and heart attack when taking HRT, but in retrospect this may have been because the women in the earlier observational studies were a healthier group to begin with.

The WHI study used a standard type of HRT comprising a combination of estrogen (0.625mg premarin) and progesterone (2.5mg medroxyprogesterone) combined in a single tablet, taken once daily, compared with placebo tablets.

The results can probably be applied to women of European extraction aged 50-65 in western countries; whether the results apply to all forms of HRT (patches, different types of progestin tablets, those on estrogen alone etc) is also uncertain, but it is probably wise to assume that the findings are generalisable.



The findings of the study indicate that:

1. HRT should not be taken with the sole purpose of protecting women against the risk of heart disease and stroke, or as a general panacea against the effects of aging
2. Use of HRT for a year or two to treat severe hot flushes or other menopausal symptoms is probably safe, and occasional women may need to stay on treatment for a longer time if these problems recur on stopping HRT. Whether some of the "natural" therapies sold over the counter will be effective and safe for this purpose remains uncertain, but they can certainly be tried if the individual wishes.

3. Local estrogen creams are likely to be safe for those with vaginal soreness or other local symptoms.

4. Some individuals at high risk of osteoporosis or fracture may, on balance, be best treated with HRT, but this is a decision to be made with a specialist or GP after bone density assessment and consideration of other treatments for the bones.

5. Some women feel generally better on HRT and are reluctant to stop treatment - again, the decision on the safety of continuing therapy is a balanced one, to be made on discussion with their doctor. The "added" risks of taking HRT are relatively small, and some issues such as the breast cancer risk can be partly addressed by regular mammography and a healthy lifestyle. Although there were more "events" in the HRT-treated women in the WHI study (19 extra events per 10,000 women treated per year) the overall mortality was no different between the HRT and the placebo groups.



Although there has been a suggestion in some studies that women with Addison's disease may have slightly lower bone density than average for age, overall there is no "special" indication for HRT in Addison's females, and their decisions should be as for the general population.

However, the age of menopause may be earlier than average in those with Addison's disease (as with the woman in the question above), and HRT may be considered. One way of looking at this is that nature usually intends most women to have normal estrogen levels up to about age 50, so if periods stop before then HRT should theoretically not increase their risk over and above that due to

nature itself. The WHI study was undertaken in women aged 50-65.

Oral estrogen tablets cause approximately a 30% increase in the "half life" of cortisol in the bloodstream (the time taken for the blood concentration to fall by 50% after a dose of hydrocortisone has been absorbed, usually in the order of 90 minutes or so). Thus, when starting HRT, women with Addison's disease may be able to slightly reduce their dose of hydrocortisone, perhaps by 5 mg or more.

Similarly, in those stopping HRT, the dose of hydrocortisone may need to be slightly increased by the same amount. Symptoms of lack of cortisol (increased fatigue, nausea, indigestion, dizziness), or a lowering of blood or urinary cortisol levels, may give an indication of this. Often very little or no adjustment is needed, but occasionally stopping HRT can lead to loss of control of Addison's disease, and adjustment of treatment is needed.

It is a good idea to have some checks with your doctor when stopping HRT, and a gradual reduction is often best, rather than suddenly stopping treatment. How gradual depends on the individual and their tendency to hot flushes etc – in general, reduction by 50% for 1-2 months, then by 50% again for the same time before stopping completely.

If there is a strong family history of breast cancer (2 or more close relatives with the disorder) then an individual's risk of themselves developing breast cancer is increased, and extra care is needed if considering HRT treatment. The individual in the question above has only one first degree relative with breast cancer, and does not require special surveillance over and above routine mammography.



Is it OK to take Addison's pills on an empty stomach?

Question 2: "Is it safe for Addisonians to regularly take their morning dose of hydrocortisone with a glass of water as soon as they awaken, on an empty stomach? I have heard conflicting advice. Would the advice be the same for hydrocortisone and for prednisone for Addisonians? On my prednisone label it says "take with food". When I talked to my pharmacist he said that's automatic from the computer, because most of the prednisone dispensed is large doses for treating chest infections etc, not small doses like Addisonians take, and large doses can irritate the gut lining. He advised me to talk to my doctor about my Addison's situation. I don't notice any difficulties taking the pills on an empty stomach - does that mean it's OK for me?"

**From Professor Ian Holdaway,
NZAN's medical advisor:**

Answer:

It takes time to absorb hydrocortisone and other corticosteroids like prednisone from the small intestine after swallowing tablets. Taking the tablets with food is likely to slow the absorption rate and delay the benefit of getting your blood levels of cortisol into the normal range. The rate of absorption varies from person to person.

Many individuals with Addison's disease feel unwell first thing in the morning until their blood level of cortisol rises after their first tablets of the day. For this reason we always suggest taking your hydrocortisone (or prednisone) and fludrocortisone immediately on awakening, with a glass of water, and wait a little before getting up.

If you are someone who doesn't notice any problems in the morning, then simply take your tablets after getting up. The water is

helpful to wash the tablets well down into the stomach so they will start working quicker.

There is no evidence that "replacement" doses of hydrocortisone or prednisone cause stomach irritation or ulcers (unlike large doses, given for conditions like severe asthma, where peptic ulcers can occur). Similarly, there is nothing to suggest that prednisone is more or less irritating to the stomach than hydrocortisone.

Nonetheless, there are occasional patients who may find that they develop indigestion after taking their tablets; this is probably because they have an underlying tendency to gastritis or ulcer trouble independent of Addison's disease. This problem should be discussed with your doctor, and options include using acid blocker tablets, or having a gastroscopy test to examine the lining of the stomach and obtain samples to see if you have a bacterial infection causing gastritis (*Helicobacter pylori*), which can be cured with special antibiotics.



Comment from Prof. Holdaway, NZAN's medical advisor:

"In hindsight, it would have been best for either Karen's husband or the ambulance officer to give the injection. There is a natural tendency to hold off if uncertain or if there is an impression that someone else with greater skill or knowledge will shortly be available. But delays often occur (traffic, the doctor is busy in A&E etc), so there's no substitute for getting the injection in early on. There's almost no chance of doing harm, whereas there's every chance of shortening the period of illness or even saving a life."

What about having in the home, electrolyte solution such as Gastrolyte, or anti-nausea medication such as Maxalon?

"I don't think these are needed routinely – but if an individual is prone to recurrent vomiting or gastroenteritis, then this could be addressed with the family doctor or endocrinologist."

Prof Holdaway answers

Joy's questions

Question 1: How long does it take the liver to process cortisone acetate before it is available for the body to use?

Answer: Within minutes

Question2: If more cortisone acetate is taken than is required by the body on any one day, will this cortisol still be available to be utilised on another day or it is expelled as waste?

Answer: It is degraded within hours and inactivated and excreted in the urine. Excess levels can occasionally cause their own problems - high BP, fluid retention, bone density reduction etc, so trying to get the correct replacement is important.

Question.3: Which adrenal hormone regulates our body temperature?

Answer: The adrenal is not involved - thyroid hormones help maintain normal body temperature.

Question.4: If I am feeling abnormally cold, is this an indication that my fludrocortisone levels are too low or my cortisone acetate levels?

Answer: If an individual is very short of either hormone then blood pressure may fall and a shock state develop in which the person may feel chilled and collapsed - but minor or modest deficiency shouldn't affect sensations of body temperature. However, everyone is different and it remains possible it could be a

warning in your case - but rather than taking extra "on spec" it would be good to get a blood cortisol level at the time to see if it is low.

From NZAN's Medical Advisor, Professor Ian Holdaway

We are including in this newsletter just a few excerpts from Professor Holdaway's keynote address at the second Northern Regional Meeting in May. Attendees had the opportunity to influence the topics covered, by submitting questions with their registration.

We hope to publish some other excerpts in future newsletters – but, no guarantees!

We encourage you to get a set of the tapes.

Topics summarised in this newsletter:

- Is autoimmunity becoming better understood?
- The genetics – how at risk of Addison's are other members of your family?
- What's the best way to check if you are on the right doses of medication?
- What do adrenal hormones do in the body?

One point Prof Holdaway clarified at the start of his address, was the convention that the hormone produced by the adrenal glands is usually called cortisol – but the chemically identical hormone taken in tablet form is usually called hydrocortisone. They are exactly the same substance. Convention can be a strange thing!

Is Autoimmunity becoming better understood?

It's a fairly common problem, medically speaking. Normally, early in our life as a foetus, the proteins in our body are recognised as "self", and the immune cells that would normally react with them are deleted so we don't start making an immune attack on our tissues.

But in certain susceptible people, these immune cells can reactivate later in life and start thinking that the body's own adrenal tissue, or thyroid tissue, for example, is foreign, and so start attacking it. Why this happens is unclear, but there is often a genetic tendency for the disorder.

Autoimmune disorders can lead to generalised types of autoimmunity (lupus erythematosus, rheumatoid arthritis, etc), or the disorder can involve just one specific tissue or organ (eg autoimmune Addison's disease.)

The damage to the tissues can be from antibodies directed against proteins in cells (such as the enzymes involved in making cortisol), or can be by "activated" lymphocytes attacking tissue cells and starting a cascade of reactions that cause them to die.

Is there anything recently known about these conditions that might be hopeful for the future?

The big thrust has come from transplant research. When you transplant someone's pancreas or kidneys, for example, into another person, the body immediately says "foreign protein" and immune cells attack the introduced tissue and normally the transplant is rejected very promptly.

So therefore a whole series of medications have been developed to try and dampen this

process down. Interestingly, cortisol itself is quite useful. At high doses it will suppress the immune reaction. Most of those who have had kidney transplants will be on a cortisol-like steroid such as prednisone at high dose to try and stop any rejection.

Recent research has used antagonists opposing the chemical mediators of immune reactions to reduce autoimmune damage (eg tacrolimus and pimecrolimus, which act on molecules involved in the process, called the cytokines; and there's Infliximab, an antibody which mops up an important chemical in the immune pathway, TNF-alpha.)

I have not heard of any studies using these agents in people with adrenal conditions. One of the difficulties in the autoimmune field is that people may seem to have the setup to get the disorder (in Addison's disease, the presence of adrenal antibodies as a marker that they may be going to get adrenal deficiency), but we know there are a number of people walking around who have got these antibodies, but never get Addison's disease. Just because the antibodies are there, it does not mean these will march on to kill the adrenal gland.)

Why this is so is not known. It would thus be a major step to test a family, see who has antibodies, and then use these drugs – which have side effects, and are expensive. You would not want to be using these drugs in people who may never be going to get the disorder anyway.

Apart from transplants, the other big area of research is people who are developing diabetes and have got to the stage where it looks like they need insulin, but they may still have about 5% of their insulin-making beta-cells left. We would like to 'hit' them as hard as possible to stop them killing off the rest of their insulin-producing cells. There isn't a good analogy in the adrenals, because by the time someone presents with Addison's

disease, virtually every cell in the adrenal cortex has been damaged. But there may be some future spin-offs from this research.

In summary - preventing immune destruction of tissues is an area where there is a lot of research going on, mainly generated through the transplant field. Screening families and perhaps doing something up-front to try and prevent the development of Addison's is certainly a possibility for the future.

The Genetics – How at risk of Addison's are other members of your family?

The incidence is about six new cases per million per year – that means about 20-25 new cases per year in New Zealand. The prevalence (the number of people at any one time who have the disorder) is between 40-100 per million adults. A prevalence of 50 would mean about 200 people in New Zealand with Addison's disease.

Autoimmune Addison's disease can occur in families, but more commonly it is "sporadic" (one-off), and the other members in the wider family tree don't have it.

60-70% of people with autoimmune Addison's disease have positive adrenal antibodies. The presence of antibodies directed against adrenal cells is a good marker early on, but they tend to disappear as time goes on.

Addison's disease is a frustrating condition to try and give counselling about. We can't be entirely sure who is at risk. The following two points are about the only useful information we can give at this time:

1. Sole Addison's disease is familial in about 1/3 cases. That is, if the only medical autoimmune condition someone has is Addison's disease, then there is about a 1 in 3 risk that another family member may develop

Addison's, or one of the other autoimmune endocrine disorders.

2. If an individual has other autoimmune disorders as well as Addison's (eg an underactive thyroid or diabetes or myasthenia gravis or some other linked condition), then about half of the family members are likely to have some autoimmune manifestations – Addison's or something similar.

It is important when giving advice about the risk for other family members, to know whether the individual has just Addison's - in which case the chances are not very high, or whether they have multiple endocrine problems, when it is more likely.

Another area linking Addison's disease to autoimmunity is the Polyglandular autoimmune endocrine disorders. These comprise combinations of thyroid problems (over or underactive), diabetes, B12 deficiency, Addison's disease etc. There are two types:

PGA-I (due to a gene defect, autosomal recessive – need two bad copies of the gene, one from each parent), and

PGA-II (can be recessive or dominant inheritance, linked to HLA-tissue type).

There are also some rare genetic syndromes which include Addison's disease – for example, adrenoleucodystrophy and adrenomyeloneuropathy, which are transmitted by the mother (the gene is carried on the X chromosome) and appear in males (X-linked). As well as Addison's disease there is damage to some of the nerves and spinal cord, and occasionally in the brain itself.

Checking that your medication doses are right for you

“This involves the art of medicine as well as the science.”

Prof Holdaway has covered this topic in detail previously (in particular, newsletter No.15, pages 13-17). The present discussion was a reminder overview. In this excerpt, we are highlighting some helpful points he made.

Reminder:The dose range of replacement glucocorticoid, per day:

Hydrocortisone 15-30mg

Prednisone 2.5-7.5 mg

Dexamethasone 0.25-1mg

A process to help you and your doctor review your hydrocortisone / prednisone and fludrocortisone doses:

A. Monitor symptoms, clinical signs, BP, weight

Are you feeling well and on top of things; any anorexia (loss of appetite); energy levels, and the like.

Clinical signs – the amount of pigmentation present; blood pressure lying and standing (more important for fludrocortisone, but cortisol does influence this a little); weight, because if you are on too much cortisone, weight tends to go up.

Assessing the replacement dose of corticosteroid is partly your own introspective look, and your doctor's assessment on talking with you about how you are. At the end of the day, that's one

of the most valuable things - so that's why it is useful to have a medical advisor who knows you, and who knows something about the disorder. It may be more important that they know you, than that they know all about Addison's, because they often will pick up on things from you or from talking to your friends, that you are just not quite right in some way. These features can be subtle.

On the over-dosage side, weight trending up a bit... but we all tend to do that as we get older, so the question becomes how much of that is due to cortisol and how much might naturally occur... Muscle weakness, thinner skin and little stretch marks that can come up if you are on too much cortisol. The under-dosage side shows as fatigability, loss of strength on formal testing of strength, BP being on the low side, etc

B. Keep a watch on bone density

Perhaps it doesn't warrant as high as Number 2 on the list, but I think that people should have their bone density measured every few years, particularly women (probably it is not so important in men). That's because a subtle feature of too much hydrocortisone is that it will make the bones a bit thinner. Normal levels of cortisol are good for bone health, but too much is bad. Measured how often? No magic answer! Pre-menopausally, there is no need to worry much, but a measurement around menopause, and after that about every 3-5 years is wise. Pre-menopause, if there are worries such as the occurrence of a fracture or a family history of osteoporosis or a need for lots of additional hydrocortisone, then get a bone density done for sure.

* A normal bone density doesn't mean that you haven't been a bit overdosed with hydrocortisone, but at least it is reassuring.

* If bone density is a bit low, that would make one more careful with replacement therapy. There are many causes for low bone density – it may be a genetic thing again – whether your parents had strong bones. If you have low bone density, it doesn't prove you have been on too much cortisone. But it is something you would want to keep a watch on.

C. Biochemistry tests.

Cholesterol - Keep a watch, it is increased if cortisol is a bit high.

Blood and urinary cortisol

There are "pros" and "cons" for measuring these. Also, these are applicable only if you are taking hydrocortisone, not prednisone or a mixture of the two (prednisone does not show up in blood assays).

Blood levels need to be related to the correct normal range for the time of day.

"Levels that are wildly out on multiple occasions would be cause for concern, particularly low levels. But a key thing to remember is that when you have low levels of cortisol in the blood, especially over just a few hours, it doesn't mean you are likely to feel unwell at that time. That's because the actions of cortisol on the blood vessels and the immune system and brain are quite prolonged. These downstream effects of cortisol usually last for many hours. You would need to have a low blood level for quite a few hours before you would feel cortisol depleted."

24-hour urinary cortisol is often slightly raised during appropriate replacement therapy for Addison's disease, and so is at risk of misinterpretation.

Are serum ACTH measurements useful? No large study suggests these are useful for monitoring treatment for Addison's.

D. Fludrocortisone dosage is a bit easier to monitor than cortisone dosage:

* You and your doctor would look at your blood pressure, and your weight. If you are underdoing the fludrocortisone a bit, you might lose a kg or two, whereas with too much fludrocortisone you might put on a kg or two because of fluid retention, sometimes with oedema (that's the pitting when you press your fingers into your ankles.)

The fludrocortisone dose is often underdone. If you are not well, then both the glucocorticoid and the fludrocortisone need addressing. (see also NZAN newsletter No.15 pp13-17.)



The Actions of Adrenal Hormones in the Body

Cortisol, a vital hormone for maintaining life, has several important roles:

- Maintains blood sugar levels in the normal range.
- Keeps blood pressure normal. It acts on the walls of blood vessels to allow them to respond to the normal chemicals that make them contract and expand as needed. In an adrenal crisis, when you lack cortisol, you can't maintain your blood pressure, not necessarily just because of the blood volume, but also because the vessels can't respond to their normal signals.
- Stops excessive inflammation. Cortisol has an immune suppression effect. The immune system is set up

to kill bacteria & viruses, and defend us. Cortisol puts a brake on the immune system, so that it doesn't "go wild". This action is especially utilised in people with serious conditions like bad arthritis or lung disease, who might be given high doses of hydrocortisone or prednisone to try and reduce the underlying inflammation of their condition. Even at normal levels cortisol has an important role in maintaining immune function.

- Maintains bone health. If we overdo the cortisone we can get thin bones, but at normal levels it has a permissive role in maintaining bone turnover.
- Permits normal brain function. Cortisol has important functions in the brain that are not well understood. It interacts with receptor sites for serotonin in the brain, for example, which allow normal brain function.
- In parallel with aldosterone, it assists with water and electrolyte balance

And cortisol has other actions too....

Aldosterone's main role is to keep blood sodium and potassium concentrations normal. This is very important, especially for potassium, which needs regulating very tightly to keep muscle function and heart function normal. Aldosterone also maintains blood and tissue fluid volume

DHEA Weak male-type hormone. (see previous articles in NZAN newsletters...)

We hope to print some more material from Prof Holdaway's address in future newsletters.

Newsletter No.20, November03:

From Professor Ian Holdaway, NZAN's Medical Advisor:

We are including in this newsletter some more excerpts from Professor Holdaway's keynote address at the second Northern Regional Meeting in May. Attendees had the opportunity to influence the topics covered, by submitting questions with their registration. We hope to publish some other excerpts, including from the Open Forum in future newsletters – but, no guarantees! **We encourage you to get a set of the tapes (see page 6).**

ADRENAL "CRISIS"

What is it?

A state where a person becomes very deficient in cortisol (and fludrocortisone) and may collapse with low blood pressure, weakness, dizziness, nausea on some occasions, and, if severe, collapse into a semiconscious or unconscious state.

What changes occur?

The low cortisol and fludrocortisone levels lead to low plasma volume in the bloodstream, and the walls of the blood vessels do not contract normally to maintain blood pressure, so the blood and oxygen supply to tissues becomes dangerously low. Infection or vomiting makes the situation worse. The function of vital organs such as the heart and kidneys may become impaired. These abnormalities reverse with appropriate treatment with hydrocortisone.

Why might a crisis occur?

1. Not enough cortisol due to poor absorption (nausea, vomiting,

diarrhoea), or forgetting to take the usual doses.

2. The usual cause is failure to adequately increase the dose of cortisol to cover major illness, particularly severe influenza, viral gastroenteritis, major infections such as appendicitis, gallbladder trouble, etc.

Emergency Treatment?

If you have any doubts, get to a hospital or A&E centre as quickly as possible – don't delay, better to be safe than sorry.

If only mildly unwell and not vomiting, take 2-3 times the usual morning dose of hydrocortisone or prednisone, and repeat 4-6 hours later. If still unwell with the underlying illness after 6 hours it would be best to see your doctor. If you feel back to normal then no further adjustment is needed. If feeling slightly below par it would be sensible to take an extra tablet of 5mg hydrocortisone or 1mg prednisone in the morning for another day.

If feeling quite unwell, and particularly if vomiting occurs, have an intra-muscular injection of hydrocortisone (Solu-Cortef) 100mg, and get to the nearest A&E centre immediately.

On arrival you or your partner/friend should inform the nurse/doctor about the Addison's disease, and whether the injection has been given or not, and say that this is an emergency requiring immediate attention (the Medic-Alert badge and/or a doctor's letter can help.) **Don't accept anything other than immediate attention.**

Immediate fluids by an intravenous drip, and further intravenous hydrocortisone should be given, and blood taken for potassium and sodium levels plus glucose values and haemoglobin and white blood cell count. Any underlying condition such as infection may

need treatment. Sometimes no apparent cause is found for the crisis event.

You may only need to stay at the clinic for a few hours if you recover promptly, but sometimes a brief admission is needed, with extra steroids for a few days.

Question: I take 15mg hydrocortisone in the morning, 5mg in the afternoon. When I double my hydrocortisone for 2-3 days because I am unwell, should I just take double the dose at the usual times? Are there circumstances when it would be better to spread it out more over the 24 hours? If so, please give me guidelines."

Prof. Holdaway answers: When unwell the body needs higher doses of corticosteroids (such as hydrocortisone) around the clock. In those taking hydrocortisone it is important to spread the doses over 3 or 4 intakes per day. Thus, in the above example, the individual could take 25mg in the morning, 10 mg at midday, and 10mg in the evening (2-3 times usual dose, spread over the day). For those taking prednisone the extra dose only needs to be taken once a day (usually in the morning) because prednisone has a long "half-life" (it lasts in the circulation for 24 hours).



Addison's Disease and "Other" Medications - interactions

There are very few medications which have a "direct" interaction with hydrocortisone or other Addison's treatment medications.

Take care with any medication that might induce nausea, vomiting or diarrhoea, such as:

- **some antibiotics** (keep a note of your own history with these)

- **some painkillers**, such as morphine, occasionally codeine, and tramadol which is a newer painkiller – some people are very sensitive to these.

Diuretics work to make you lose fluid - with most of them you lose potassium as well, and also deplete yourself a little of salt. Monitor weight and serum potassium and sodium carefully in case some extra potassium (usually as "slow K") is needed.

"NSAID" pain killers such as Voltaren, Brufen, etc can cause fluid retention and act like extra fludrocortisone. Watch blood pressure and weight.

Preferably, try something else as a painkiller – such as paracetamol (Panadol), aspirin, acupuncture.

We tend to underplay the simple remedies, like paracetamol, which is an extremely safe agent, because we don't take enough of it, and too quickly we say it is not effective.

For paracetamol to be effective, you need to take 2 tablets every 4 hours, whether you have the pain or not. People tend to let the pain build up, such as headache or joint pain, saying they don't want to take too much of the painkiller, and by then the pain may have become quite severe. If you take paracetamol regularly, pain or not, when you have a bad migraine, sore joints or a bad back, and take it round the clock for a couple of days (while awake), it suppresses the pain, and you'll likely be able to get off it again.

Paracetamol is useful for keeping the body temperature down when you have flu and the aches.

Oestrogens (in the oral contraceptive pill or in HRT and some "natural" menopausal remedies) slow the rate of clearance of cortisol from the body, so the cortisol

replacement dose may reduce by 25-30% when commencing an oestrogen preparation.

A few medications speed up the clearance of cortisol from the body, so the dose of cortisol may need to be increased. However, it is unlikely that the average person with Addison's will ever need these medications:

- **Phenytoin (dilantin)** – for epilepsy
- **Rifampacin** – for TB treatment



(See accompanying story in newsletter 20, Jeanette's salt solution)

Professor Holdaway comments on salt intakes:

Individuals with Addison's disease lack the hormone aldosterone, which normally acts on the kidneys to retain salt and maintain the blood volume and blood pressure. Untreated Addisonian individuals can thus have low blood pressure and sometimes a low blood sodium level (salt is sodium chloride). Fludrocortisone is a synthetic form of aldosterone and acts to reverse the effects of aldosterone deficiency. The blood renin level is a sensitive marker of whether or not the blood volume and dose of fludrocortisone is OK.

Usually, Addison's individuals should follow normal health guidelines and take moderate or lowish levels of salt. A more liberal intake is needed if the blood pressure is low, often with feelings of faintness, or if the renin is high despite usual doses of fludrocortisone, or if the person is in a hot climate when salt loss is increased.

Jeanette did the right thing by taking some extra salt when in Tahiti, but once the need for this was over the extra salt began to have

adverse effects, and in particular it expanded her blood volume too much and drove her blood pressure up. Some individuals with hypertension (high blood pressure) are very sensitive to increased dietary salt, and it is better to keep the

See accompanying story in newsletter No.20, "Drink enough fluid but not too much":

Professor Holdaway comments about fluid intake: There is a current fashion for individuals in NZ to carry extra water and take very liberal amounts which sometimes causes problems with kidney water conservation. In general, it is better to take extra water/fluids only when increased thirst occurs.

Newsletter No.21, March/April 04:

From NZAN's Medical Advisor

Professor Ian Holdaway:

Addison's Disease and Other Medications - interactions.

In Newsletter No.20, Nov 03, we published material on this topic from Professor Holdaway's talk at the Northern Regional Meeting in May03:

Prof Holdaway pointed out that NSAID pain-killers such as Voltaren and Brufen can cause fluid retention and act like extra fludrocortisone.

One of our readers has asked whether this applies also to the "second generation NSAIDS", the COX-2 inhibitors, that are available for people with arthritis, etc.

Prof Holdaway's response is: "The COX-2 inhibitors such as Vioxx, Celebrex and Arcoxia all cause the same effects as typical NSAIDS in terms of fluid retention etc, although they are less likely to cause gastric upset. In general, these agents (NSAIDS and COX-2 inhibitors) may be OK in many instances, so it would be wrong to give the impression that they must never be used - just that caution is needed and any swelling of the ankles, general fluid retention, or weight gain should be reported to the GP."

We are reprinting all the painkillers interactions information together in the box on this page:

Take care with any medication that might induce nausea, vomiting or diarrhoea, such as:

- * some antibiotics (keep a note of your own history with these)
- * some painkillers, such as morphine, occasionally codeine, and tramadol which is a newer painkiller - some people are very sensitive to these.

NSAID pain killers such as Voltaren, Brufen, etc can cause fluid retention and act like extra fludrocortisone. The same applies to the COX-2 inhibitors, Vioxx, Celebrex and Arcoxia. Watch blood pressure, and weight.

Preferably, try something else as a painkiller - such as paracetamol (Panadol), aspirin, acupuncture.

We tend to underplay the simple remedies, like **paracetamol**, which is an extremely safe agent, because we don't take enough of it, and too quickly we say it is not effective.

For paracetamol to be effective, you need to take 2 tablets every 4 hours, whether you have the pain or not. People tend to let the pain build up, such as headache or joint pain, saying they don't want to take too much of the painkiller, and by then the pain may have become quite severe. If you take paracetamol regularly, pain or not, when you have a bad migraine, sore joints or a bad back, and take it round the clock for a couple of days (while awake), it suppresses the pain, and you'll likely be able to get off it again.

Paracetamol is useful for keeping the body temperature down when you have flu and the aches.

Aspirin is reasonably safe from the viewpoint of fluid retention, but can cause gut irritation or indigestion or occasional bleeding. Paracetamol is probably the safest overall.

Q&A from the Open Forum session at the Second Northern Regional Meeting in Auckland, May 2003:

There was lively discussion, with Professor Holdaway answering a wide variety of questions from participants. Here are some of them

Question 1:

Does the Solu-Cortef injection have a fludrocortisone component in it?

Prof H: No, it's just hydrocortisone, but as we mentioned hydrocortisone has a little bit of fludrocortisone-like action so you do get a slight double whammy effect. But in the serious illness situations, it's the cortisone lack that's the key thing. So you don't need to worry about the fludrocortisone.



Question 2: What's the best time of the day to have blood taken for renin, sodium, potassium, DHEA?

Prof H: For renin, sodium and potassium timing doesn't matter. For DHEA (the blood test is DHEAS, the sulphated form), if you are not on the capsules and are just having a basal level done, it's better to have the test in the morning between about 8 and 11. That's because there is a slight rhythm through the day with higher levels around that time. If you are on the capsules and you want to know if you achieving a good level, have the test about 2 to 4 hours after you've taken your capsules.



Question 3: What about the long term prospects for people with Addison's?

Prof H: So long as replacement doses are at a correct level, then your long term health should be as good as anyone else's, and also your longevity. There have been one or two studies of how long people with Addison's

disease live, and it doesn't seem to impair life expectancy.

Q...So, other immune disorders that come are because you've got a predisposition to autoimmune problems, not because you've got Addison's?

Prof H: That's quite a good point, it is true that people who have the autoimmune form of Addison's disease can get other sorts of autoimmune conditions as well. They can come on later in life, so it's variable, sometimes the Addison's disease will come first and then someone might develop a thyroid condition five years later, and occasionally some other disorder such as diabetes a few years after that. So, your doctor and yourself do need be a bit alert to subsequent health problems but as you saw in those percentage figures the percentage chance of getting associated conditions isn't all that high [reference to previous newsletter]. You've got a better chance of not getting any other sort of autoimmune condition than you have of getting an extra one.



Question 4:

Was it an Addison's crisis?

One participant's dialogue with Prof Holdaway was an opportunity for everyone present to learn.

Q...I went to my doctor with a bad run of migraines. My 3-monthly blood tests had been done the week before, but they couldn't find any results from those, so my doctor said, we'll do those again now.

That was on a Wednesday afternoon at 12.30, my husband found me unconscious at 6.00am the next day with what the hospital has told me was an Addison's crisis. But my GP says she cannot see that it was Addison's crisis because the blood test taken less than 24 hours before showed a normal cortisol level. It's made a bit of a barrier between us

because I think I have to go by what they told me in the hospital.

Prof H: So you were semi-conscious, and had to be taken to the hospital, and you were given extra cortisone and you recovered quickly?

Q...Well, I was there for five days, before they got me back to normal.

Prof H: So the key question is whether it was just solely a lack of cortisol or whether it was the very bad migraine or something else. I think it sounds like an Addison's crisis to me, and as we've heard discussed here these things can come on surprisingly quickly in some people. Normally you know if you are unwell, and you have time to get your treatments underway. But just very occasionally cortisol lack can be quite rapid. Do you have much recollection of what led to your ending up on the floor?

Q...None at all. I went to bed the night before feeling groggy because of the migraines, but I had taken all my Addison's medication that day.

Prof H: Yes, and then at six in the morning you were found on the floor ...

Q...In another room, yes.

Prof H: I think you just ran out of cortisol overnight. The fact that your blood measurements were normal 18 hours before doesn't faze me too much. We've mentioned cortisol's short half life, and how quickly the level does decline. Because of the severe migraine, you had the extra demand for cortisol, so it was a true crisis.

Q...Thank you.



Question 5: For the past 14 months I have had low potassium levels despite taking extra potassium chloride. Any ideas?

Prof H: Yes, obviously the first thing one would worry about is the fludrocortisone dosage, whether that's set a little high. Are you on fludrocortisone? Some people taking average replacement doses will get a potassium losing state that I previously mentioned. It's a natural action of fludrocortisone to make you lose more potassium in the urine. If you are on average doses then that's usually balanced out by your diet and so on, but some people are quite susceptible to a fall in potassium levels.

One would normally measure the amount of potassium in a 24-hour urine collect. If it's high that proves that you are losing it that way and the only real answer is to step up the potassium replacement. You're not on any other tablets that would affect potassium levels?

Q...A calcium channel inhibitor, Cardizem.

Prof H: That shouldn't do it. No diuretics or anything like that? If your blood pressure and general health are good, your doctor could lower the fludrocortisone a little bit in case you are on a wee bit too much and that's making potassium loss worse.

Q...No diuretics. On the three occasions over the years that I have tried to lower my fludrocortisone, I have had severe attacks of vertigo a few days after I've lowered the dose.

Prof H: Right. I think it's sensible to just stay on your present dose then.

Q...I thought that.

Prof H: Nuisance as it is, you just have to crank up the potassium replacement. Do you take Slow K?

Q...Yes

Some people need surprisingly large amounts to get the potassium normal. It is an important thing to do though, so it's good that you are watching it. That's sensible.

Q...Thank you.



Question 6: Hiccups!

Before I was diagnosed with Addison's I used to have quite serious periods of hiccups. They would go on during the day. I'd wake up with them during the night. Now I've read in overseas publications this could be a symptom of Addison's. Is this recognised or is it just a coincidence?

Prof H: If you look at the lists of the symptoms people get with Addison's, you are right, I think hiccups are there. But it's rare - it seems 1 to 2% of people may have hiccup problems when they first present with Addison's.

Severe ongoing hiccups is a very rare problem, but can be very difficult to treat. Interestingly, one of the treatments that sometimes works for intractable hiccups (in studies where people didn't have Addison's disease) is a big shot of intravenous hydrocortisone! So there is something 'unusual' about steroids and hiccups, but it's pretty rare. Do you get them nowadays?

Q...No.

Prof H: So it was only before the diagnosis? When you started your replacement treatment they resolved, they went away?

Q...I can't remember back that far. It's going back nearly 40 years. I had never mentioned it to anybody because it wasn't a concern.

Another participant: Yes, definitely hiccups was a symptom for me too! And it was before

diagnosis, while I was having a period of feeling really low and maybe being in bed or off work because I was so sick - and always the hiccups. In fact it was almost an indicator that I was getting to be low. As soon as I started taking hydrocortisone I haven't had the hiccups at all since.

And another participant: I was a hiccuper too!



Question 7: Is thirst a side effect of Addison's or is it a slant towards some other problem?

Prof H: I think only if your steroids are quite under-replaced. If you are quite short of cortisol, and if because of that your blood volume is a bit contracted, then you may get a thirst switch on to try and build up your fluids. It's a bit of a rare one - you wouldn't normally expect to have an accelerated thirst if you're on standard replacement.

Thirst is usually not a medical problem. Folk who are big drinkers of fluid can get into a sort of vicious circle when they drop their fluid intake a bit - then they feel thirsty and want to keep drinking. Severe thirst, of course, has to raise a suspicion of something like diabetes, but mild thirst is probably just an innocent bystander.

Thirsty constantly? Well there are rare problems that make you very thirsty. There's a condition called diabetes insipidus (quite different from diabetes mellitus) which occurs when hormones that are involved in concentrating the urine don't get produced. But that's not a part of the syndromes associated with Addison's disease, so it would be a real bad luck scenario to have two different conditions going on at the same time. But it is possible, and what we do for people who have major thirst, and it's a real problem, is do a test called an overnight water deprivation test. They don't have any water overnight (it's pretty tough for them), and none in the morning, then they come to the clinic and have their urine tested to see how

concentrated it is. If they can concentrate the urine normally then there's no background problem it's just a switch on of thirst of an innocent type. But if they can't concentrate the urine properly then there's a problem. They've got either pituitary or kidney disease. So it may be worth checking it out if constant thirst is a nuisance problem.



Question 8: I have Addison's and I am concerned about my child's risk.

My question relates to the inheritance, the genetics of Addison's, which you have already spoken about. I've got Addison's and three young children. One child in particular I have just a mother's gut feeling about. He is very slow to recover from sickness, and he has got some pigmentation in places, like elbows, where I still have it. Are there tests that can be done to relatively easily detect whether there is a proneness to Addison's, or whether he may develop it.

Prof H: The key test, the important test, is an adrenal stimulation test, which you probably know about, the "short synacthen test". For that we use a form of ACTH called synacthen which is very quick acting. So although kiddies aren't terribly keen on tests, this one is not too big a deal. It's a baseline blood cortisol, then a little injection can be given through the same vein that the blood's taken from, of this ACTH which will stimulate the adrenal and then 30 minutes later you take another blood for cortisol, and should get a normal increase in the blood cortisol in response to the ACTH. It's very sensitive, very reliable, it's how we diagnose the condition.

There's no point in doing it once you've got an established diagnosis because you'll just have a flat response. But if there is concern about a child or a relative you think could have Addison's, that's the test to do. If you

ever said to your doctor how about a short synacthen test, he or she would know what you are talking about. GP's can order the test through the private laboratory. However, the private laboratories tend to do a high dose test which takes 60 minutes – they are not quite as used to dealing with kids. The major hospitals do the test, and there's our service at Auckland Hospital, you can have it done as an outpatient, it's very simple. Karen [endocrine nurse specialist, also at the meeting demonstrating self injection with Solu-Cortef] as you can see is fantastic with children, and so it's probably better to just get your GP to send us a note at Auckland Hospital to do a test on a child.



Question 9: About the speed of development of Adrenal Crisis, and the likely relationship with one's usual blood pressure levels...

Karen: You said that some people are prone to crisis much more quickly than others. I was diagnosed in a crisis and then just a couple of months ago I had another crisis. And it was very quick - within a period of three hours I was practically semiconscious on the floor, at home with three young children. So is that something that does happen to others, or is it more peculiar to me, that when I go, I go?

Prof H: It is unusual to have it hit you with such speed, although it's been mentioned several times here today how some people have gone into a crisis situation very quickly. But it is unusual and raises the issue of whether there's some other factor, it might be the dosing of your tablets needing to be adjusted, particularly the fludrocortisone. I imagine since this has all happened to you, people have taken a lot of interest in your replacement and whether it's adequate etc? What sort of schedule are you taking?

Karen: I'm taking 15mg of hydrocortisone in the morning and splitting the afternoon dose,

so 5mg at about 12.30 and 5mg at 4.30, and half a Florinef.

Prof H: And if you go higher in the Florinef you're not so good?

Karen: [hadn't tried higher Florinef - see below**]. For about a year I've been having quite dizzy light-headedness. My blood pressure is on the low side, but OK.

Prof H: Because of that, I think you're a bit under-replaced with the fludrocortisone, and we've pointed out [e.g. NZAN Newsletter No.15, pp 15-18] there's been a bit of a tendency for doctors to not quite give enough, then it makes you susceptible to get the cortisol crisis effects because you start with a somewhat lowered blood pressure and electrolytes that perhaps aren't quite right. So it may be worth going up to a slightly higher dose of fludrocortisone, and then if you still have more crises, possibly consider going over to prednisone instead of hydrocortisone, because of it's longer half life in the body.

Lyn: Is there a possibility that having normal or low blood pressure could be a trigger for quicker crisis, because Karen and I share that in common. I take my hydrocortisone 30mg all at once in the morning, and 0.2mg Florinef daily. [Lyn is a keen bike rider, who does everything at "ninety miles an hour"!]]

Prof H: Yes, I think that's probably quite a good point, isn't it? Some individuals who don't have Addison's, particularly women, do run quite low blood pressures. People often get worried about it, but normally low blood pressure's a great thing! It means you're probably going to have an excellent life expectancy, compared with the effects of having high blood pressure! So I always reassure people whose blood pressure is naturally around 90/60, even though, true, in hot weather they might get a bit faint and dizzy. I haven't heard it addressed scientifically but it is quite possible that if

you've got this natural low blood pressure then you are sailing a bit closer to the wind if you have cortisol deficiency. You haven't got the reserves of someone who's normally got a blood pressure of 130/80 - they can tolerate dropping their blood pressures by 20 millimetres of mercury a lot better than you can, because if you drop from 90 systolic you're only 70 systolic and that's when you're definitely beginning to feel pretty weak. So that is an interesting point. All the more reason to pay attention to the fludrocortisone dose



Newsletter No.22, August 04:

From NZAN's Medical Advisor, Professor Ian Holdaway:

Question 1: Three ladies at the Christchurch meeting were having difficulties due to prolonged anaemia. Does Addison's contribute to this?

Answer: Anaemia may occur in untreated Addison's disease, but shouldn't be a problem if treatment has been given. There's a higher incidence of vitamin B12 deficiency and hypothyroidism (underactive thyroid), which can cause anaemia, so these should be excluded. Other unrelated causes of anaemia such as iron deficiency should also be checked. A haematologist may need to be consulted.

Question 2:

Addisonians get the message that osteoporosis is a risk from slightly excessive glucocorticoid replacement, but that not all individuals with Addison's disease are equally at risk. So they are advised to get a bone mineral density test, and then "take it from there."

Steroids like hydrocortisone and prednisone are known insulin antagonists, but the message isn't usually given to people with Addison's disease that impaired glucose intolerance or overt diabetes mellitus is also a risk for them if their dose of steroids is a little bit high.

Under what circumstances should people with Addison's disease also have their blood glucose checked?

Answer: If high dose steroids are needed for long (>4 week) periods then diabetes can occur, especially in those who are genetically predisposed (positive family history). Individuals with Polyendocrine Autoimmune syndromes (especially Type 2), are also at risk and should be watched with fasting glucose values now and again. Sporadic Addison's individuals shouldn't be at greater risk of diabetes unless they also need routine high dose steroids for other medical conditions.



NZAN surveys have shown that about 20% of our Addison's members also have another endocrine autoimmune disorder such as an underactive thyroid gland or diabetes. This means they have "Polyendocrine Autoimmune syndrome Type 2".

Professor Holdaway reminds us:
"Monitoring thyroid function should also be part of the ongoing management of people with Addison's disease, especially if there are symptoms such as increasing tiredness, intolerance of the cold, weight gain or fluid retention."

At the beginning of September, Professor Holdaway is attending the 12th International Congress of Endocrinology in Lisbon. He is an invited speaker at a symposium about new developments in understanding acromegaly, adult growth hormone deficiency, and traumatic brain injury - the common thread is the growth hormone/IGF axis. Professor Holdaway's paper is about the consequences of IGF-1 deficiency and excess.

ICE congresses are held every four years. The first was in Copenhagen in 1960. The ICE 2004 website makes clear the size and scope of the congress: "Over 55 invited symposia will cover the latest cutting-edge basic and clinical topics delivered by experts in the field from over 25 countries."

We look forward to some feedback about the conference, in a future newsletter.