

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

### **Contributions to Update Newsletters July 2001 – July 2002**

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## UPDATE NUMBER 13, JULY-AUGUST 2001

### INTRODUCING PROFESSOR IAN HOLDAWAY

Professor Ian Holdaway (MD FRACP BMed Sc) has been actively supportive of NZAN since the start, and we are fortunate that he is willing to share his extensive clinical and research experience for a term as medical advisor. He is currently head of the Department of Endocrinology at Auckland Hospital.

Professor Holdaway graduated in medicine from the University of Otago. His early postgraduate training was at Auckland Hospital, mainly in the Medical Professorial Unit and the Department of Endocrinology. He held research fellowships at Auckland Hospital, St Bartholomew's Hospital in London, and the University of Manitoba in Canada.

He then returned to the Department of Endocrinology at Auckland Hospital, and the Department of Medicine at the University of Auckland School of Medicine.

Professor Holdaway has made significant contributions to research and scholarship in Endocrinology, and has been awarded many major research grants, held many guest lectureships, and authored over 120 published papers. He has served on many committees and organisations, including the Auckland Medical Research Foundation, the Medical Research Council of New Zealand Clinical Assessing Committees, the Cancer Society of New Zealand, and as President of the New Zealand Society of Endocrinology. He also sees some private patients.



### SOME MESSAGES FROM PROF HOLDAWAY'S KEYNOTE ADDRESS AT THE NORTHERN REGION MEETING:

We have transcribed some sections, to retain the clear conversational style.

#### THE VALUE OF NETWORKS

Prof Holdaway believes networks like NZAN have value for Addisonians. "Join a group, learn about your condition so that you know more than your doctor, and certainly more than a person at A&E if you turn up there in a crisis, so that you [or your support person] can tell them what the situation is, and what has to be done. The more people know about the conditions they have, the better. The old days of "let the doctor look after it, he'll know what to do" are pretty much gone. It's an individual arrangement between you and your medical advisor, and (with a smile) sometimes it's a moot point as to who knows more about the condition. Because Addison's is an unusual condition, there are many GPs who are not well up on the management of Addison's disease.

“Support groups disseminate what is known about the disorder, and new research findings etc. They encourage members to keep records, and to get copies of letters from their doctor. Make the most of appointments with your specialist – when you think of questions, write them down and take them with you and ask them. It’s a good idea to take a friend – two pairs of ears can be better than one.”



## **ADRENAL GLAND HORMONES – what they do and how they are regulated**

The adrenal glands have an outer cortex, and an inner medulla. In Addison’s disease both areas are usually damaged. Prof Holdaway gave a clear explanation of the hormones made in the adrenal glands –cortisol, aldosterone and adrenal androgens in different zones in the inner cortex, and adrenaline and nor-adrenaline in the outer medulla. He showed with slides the tidy system by which cortisol and aldosterone production are regulated by feedback loops in a person without Addison’s.

“Most importantly, the inner zone of the cortex secretes cortisol – an essential hormone for life. When you try to talk to people about what cortisol does, it’s always a bit tricky, because it acts on virtually all cells of the body - there are receptor sites on the nucleus of cells right through the whole body. It mainly enhances proteins in these cells that are important for energy pathways – for glucose metabolism, and getting energy into the muscles and liver etc. It is very important in stress. It is often called one of the “stress hormones” because [in non-Addisonians] it goes up under conditions of stress and enables our bodies to fight infection and inflammation, and toxic effects and so on, so you need cortisol to defend yourself against attack from illness. For replacement we usually use cortisol itself – hydrocortisone is another name for that.”

“The cortex also makes aldosterone, the hormone that retains salt. You need aldosterone to keep your blood pressure up, and the normal sodium and potassium levels in the blood. If aldosterone is deficient, it is replaced with a synthetic form called fludrocortisone (Florinef). This does the same job as aldosterone.

“The inner part of the adrenal, the medulla, releases adrenaline and a bit of noradrenaline. They are the fight-flight hormones that make you run fast when a bull is charging towards you, it revs up muscles. It is one of the few hormones that acts in a very quick way, in a few seconds, or a minute, to have its effect. Most of the adrenaline in the body comes from nerve endings, so if the adrenals are not there, there are other places that make it and you still have fairly normal levels of adrenaline, so don’t have to replace it”



## **DHEA – worth considering, especially for women**

Prof Holdaway reminded us that all the steroid hormones are made from cholesterol. Although they all have different key functions, there is also a bit of overlap. Progesterone, for example, shares a bit of mineralocorticoid activity.

“DHEA is one of the steroids made from cortisol, and is a weak androgen, which means it has weak male hormone effects. It circulates as a sulphate, so is more commonly called DHEAS. It is one of the hormones which have excited interest because levels in the body fall with age (like growth hormone, testosterone, oestrogen). At 70, people have only 20% of the levels they had at age 20. Having observed that, people said, is that natural, is that what we should be doing, or might it be better to keep these levels high so they don't fall with age? Would that make us all live forever? Or make us all feel better when we got older?... So that is a fertile area of research. The answer to that important question is not known. We are not really talking about that issue now – rather, we are talking about the fact that in Addison's disease the levels are very low, particularly in women, because the adrenals are their only source. You don't find such a low level of DHEA in men with Addison's, because the testicles do make some. And males have a lot of testosterone that dominates DHEA. But in women it can be quite an issue if their DHEA is low.

There has been a range of studies, most of which have been reasonably positive. It is not a miracle drug, obviously – otherwise everyone would be on it. But it definitely seems to have some benefits. There have been several dose finding studies – it seems about 25-50mg a day gives best effects. If you go too high, especially in women, you start getting side effects, and those side effects are just what you'd expect if it is a male pattern hormone – a bit of acne, slight increased hair growth around the moustache and chin area, slight muscularity increase, although that might be good for strength.

Virtually all the studies are in women. It's really been in the psychological area that the biggest push has been – it seems to have increased well being, reduced depression, and improved sexuality. Libido and sexuality in females, something that endocrinologists have to get involved with a bit, is a pretty tricky area, because many things are involved in libido and sex drive, how happy you are, what your relationship with your partner is like, your finances, everything really, but it is hormonally driven, oestrogen from the ovaries has a role, but in women probably male hormones like DHEA have a definite role, they seem to enhance sex drive in particular.

And so not surprisingly when DHEA is given, and questionnaires are done and a proper double blind studies are performed, it does increase sex drive and sexual responsiveness in many, although not everyone. It has subtle biochemical effects. It produces extra growth factors like IGF1 (insulin-like growth factor 1) - it increases that a bit which ups muscle strength and endurance. And it has good effects on your cholesterol - it ups your good cholesterol, the high density form (HDL) that you want, that sucks the

cholesterol out of your arteries and back to the liver; and it lowers the bad cholesterol, the low density lipoprotein cholesterol.

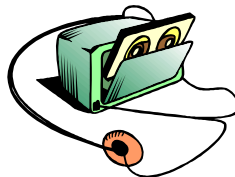


The side effects in those that experience them are usually very mild. In fact, when you look at the formal studies, it is very rare for people to drop out because of side effects - whereas if you look at a blood pressure study or a cholesterol lowering study, you find 10-15 % drop out because of side effects. Should everyone be on it? There isn't an answer to that. For those who feel well, there is probably no particular need to be considering it. For those women who feel that they are not sort of balanced right, then why not, you might have a trial. (Jeanette will know more about getting hold of DHEA in NZ. It is getting easier, but it is not funded by the government.)"

Professor Holdaway presented some slides from a publication in a medical journal. "This shows a global psychological health score. These are properly done studies, with a placebo so you don't know, and the doctor doesn't know, if you are on the active tablets or not. People take this for 4 months, fill out questionnaires before and after 4 months of treatment. For those on placebo their well being scores stay about the same, as you'd expect. If you are on DHEAS, then after 4 months, your global psychological well being is improved by about 30%, a highly significant change.

Similarly, if you look at depression - for those taking DHEAS there was almost a 50% improvement in factors that are depressive in nature. So there was clearly less tendency for depression on that agent.

That was a short study. What happens when you take it for 2 years, does it wear off? We don't know. So many things affect how we feel in life... But this trial result is as good as you'd ever see with an anti-depressant tablet, that's for sure."



### **OTHER COMPREHENSIVE TOPICS TO HEAR ON THE TAPES:**

- Fine tuning the best replacement strategy for you – with comment on the different approaches in different countries. New Zealand mainly uses hydrocortisone and prednisone as the glucocorticoids; Australia uses some prednisolone instead of prednisone; some parts of the US are tending to favour long acting steroids like prednisone and dexamethasone.
- Blood and urine tests that are sometimes used for monitoring dosage appropriateness – which are useful (eg renin), which are usually less useful (eg cortisol), and why.
- Guidelines for when to increase doses of hydrocortisone (or prednisone) and fludrocortisone,

- Dealing with emergencies – including the importance of responding quickly and seriously to vomiting illnesses; how to be taken seriously in an emergency.

And more.....

Prof Holdaway included in his talk, some material from a recent review for endocrinologists about treating adrenal insufficiency. On the US-based Web Site [www.uptodate.com](http://www.uptodate.com) is a section which doctors access by subscription, and also a Patient Resource Centre, with free access to detailed articles - for example, "Patient information: Adrenal insufficiency", which complements the review that Prof Holdaway discussed.

We think it is important to point out to NZAN members, however, that the glucocorticoid regimes favoured in that article are not universally adopted outside of the US, or indeed used in other parts of the US. As Dr Braatvedt has also said in his answers to members' questions, there is no consensus about which replacement glucocorticoid is best for people with Addison's disease. The crunch test is wellness - if you don't feel well, it is worth talking with your doctor about switching from one to another type or dosage of steroid agent, or changing the timing.

## **PROF HOLDAWAY'S SUMMARY SLIDES:**

### **Highlights of the last 5 years in research on Addison's disease:**

- **Increasing use of long acting steroids for treatment (mainly USA)**
- **Osteoporosis research**
- **DHEA**
- **The genome project**

### **Challenges for the next 5 years in research on Addison's disease:**

- **Further improvement in treatment and monitoring:**
- **Gene therapy**

### **Transplants**

## UPDATE NUMBER 14, NOVEMBER 2001

### FROM DISCUSSIONS WITH OUR MEDICAL ADVISOR, PROFESSOR IAN HOLDAWAY:

\* **A few people may have a confusing “de-energising” response to DHEA**, because of opposing interactions with other steroids such as estrogen, and consequent effect on cortisol clearance. Trying a reduced dose of DHEA may be the simplest way to solve this. Interactions between medications for Addison's disease and other treatments will be the subject of a review in an upcoming newsletter.



\* **Which is more common – primary or secondary adrenal insufficiency?**

At the Auckland regional meeting in July, Prof Holdaway mentioned that primary adrenal insufficiency (adrenal cause) is rarer than secondary adrenal insufficiency (pituitary cause). Noting that about 85% of NZAN members are “true” Addison's, Jeanette followed up.

“The prevalence of Hypopituitarism is estimated at 100-150 patients per million, with about 10-20 new cases per million per year. Addison's prevalence is 40-100 per million (Clin Endocrinol 41;757, 1994 and Lancet,2;744, 1968), and new cases about six per million per year,” said Prof Holdaway. “My impression is that secondary adrenal insufficiency would be about three times more prevalent than primary adrenal insufficiency in New Zealand.”

That “secondary” figure doesn't include people with adrenal suppression from medical use of corticosteroids, quite a large category, mainly those on long term steroids for asthma, chronic obstructive respiratory disease, and rheumatoid arthritis.

“Because these individuals retain normal aldosterone production, and because their stress responses are sometimes partly preserved, people with secondary adrenal insufficiency are less likely to get into medical problems, and NZAN may be seen by them as less relevant – although much of it is,” says Prof Holdaway.

## **MORE EXCERPTS FROM PROFESSOR HOLDAWAY'S ADDRESS at the July Regional Meeting in Auckland:**

### **When the usual daily dose of steroids isn't enough:**

"Correct treatment in emergencies, in major illnesses, surgery and so on, really is an important issue. That's why you have a Medic-alert bracelet, and lots of information about your condition, because this is a time when Addison's can really harm you badly, if it's not handled properly. Occasionally fatalities will occur because people don't recognize that Addison's disease is present in a very ill individual, or don't treat it appropriately.

"There are mechanisms in the brain that recognize stress and signal the pituitary to release more ACTH so that the adrenals make more cortisol. People with Addison's can't do this. They need extra cortisone by injection – or, in some circumstances, extra tablets will be enough."

Prof Holdaway gave his perspective, commenting also on a recent US review (UpToDate).

"So again there are multiple ways of dealing with this, and a number of suggested guidelines have been developed around the world.

"**Major illness** is usually relatively easy to define, there is no doubt about illness severity, e.g. traffic accident, broken leg, in hospital for an operation – you need high amounts of cortisone, that is usually given as hydrocortisone intravenously every 6-8 hours - there are treatment protocols, and doctors are soon involved.

But what about emergencies where you are, for example, sitting in the middle of Thailand with vomiting and diarrhoea - what are you going to do?. In those circumstances, prompt injection of steroids, by oneself or a companion, is very important – see box.

### **Responding to vomiting and diarrhoea**

**"An important issue for people with Addison's disease, is knowing and taking the right action, if an attack of vomiting and diarrhoea hits – which may be when one is out on a walking track, or in the middle of a third world country, or in a culturally different medical system, for example. Vomiting can quickly become a serious problem for people with Addison's disease.**

"If you can't keep your tablets down, you can become cortisol deficient very easily. That's bad enough, but you also get volume deplete very easily. The fluid in vomit comes not just from what you have eaten, but it's also actually being sucked out of your circulating blood volume to some extent, so people with Addison's disease that are vomiting can get dehydrated, blood pressure falls, and they collapse quite easily. Diarrhoea can do the same thing.

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"If you are very nauseous, quite often the stomach won't pass on the tablets terribly well to the digestive tract, so even nausea without vomiting can be a problem, because you don't get the tablets down into the intestine where they get absorbed.

"So vomiting illnesses have to be treated quite seriously and that's where the injections do have a definite role. It's

pretty commonsense that if you are severely ill or injured, someone has to inject the steroids into you. The important point to remember is, if you are 'just' vomiting and ill, injections are also quite helpful."

Discussion followed, on what point to take action. "I think if vomiting is fairly soon after the tablets were taken (about an hour or so) I would prefer to give an injection after that because those tablets have probably not been absorbed, there is a stress illness, and the individual needs extra anyway. If the vomiting is in the afternoon, and you have had your morning tablets OK, then you could possibly wait a bit and see if it settles down, but if there was a second vomit you might want to use cortisol injections then...

"So hopefully most of you will go through your lives, never having to have injected hydrocortisone - but again, it's better to have it and not need it, than to need it and not have it."

**Moderate illness** – quick to say, difficult to define. Professor Holdaway noted that for moderate illness, the US review favoured quite a lot of extra steroid, 100mg hydrocortisone a day (50mg morning and evening), or an intravenous shot. Double or triple the daily dose is the usual advice in New Zealand. But what is a moderate illness?

Prof Holdaway suggested the practical guideline, "It's something you'd go to the doctor about – bad 'flu, a foot that's very sore after dropping a brick on it... If you are in doubt, take it, you won't do yourself any terrible harm with a day or so of extra cortisone that you may not have really needed."

"If you are so sick that you can hardly get out the door to see the doctor, I agree you really need it."

Prof Holdaway described a problem we can all have: "You can sit around in a room like this and say 'This is what I will do!', but when you actually do get sick, you forget, or you just can't be bothered taking this extra stuff, and you can get into trouble if it is not taken, that's for sure.

"For minor procedures, having a barium meal, an endoscopy, a gastroscopy, an MRI scan, no extra steroids are usually needed but if you are a bit worried about it, take a bit extra – it's in your hands... Dental procedures can be both psychologically and physically stressful, so I would take a bit extra.

“The downside of taking the extra steroids over a short period of time is not great. If you are someone who has other chronic illness or stress, so you are doubling up doses every second day, then it's very easy to get into a pattern of over-dosage. But if it is a now and again issue, a nasty cold, wondering if it is 'flu, should I be taking extra cortisol, what should I do, what shouldn't I do – if you are feeling actually fine in yourself and pretty bright on it, you probably don't have to take extra, but if you are feeling any doubt, take it.

**“Anticipation stress and psychological stress** are two issues I am often asked about. Those are very difficult questions and in some ways it is your own prior experience that might tell you what's best.

“If you know something is coming up that will put a bigger demand on you, what should you do with your steroid doses? If you know that when you have climbed Mount Ngauruhoe, or when you've done something extra, that you felt pretty unwell, then I would take a bit of extra steroid in anticipation of any similar upcoming major issue. If you have no idea at all whether this upcoming stress, perhaps a big job interview, is going to put a high demand on you, then that is difficult - if you are worried, by all means take a bit extra, such as 5-10mg hydrocortisone.

“Virtually all of the guidelines say that psychological stress is not an indication to increase your dosage, that in general you do not need extra cortisone, but I don't entirely agree with that. If your spouse suddenly keels over and dies that's an awful stress and if you measured cortisol levels in everyone in which that happened, the remaining spouse's cortisol levels would certainly go up for quite a bit of that day.

So I do not think it is unreasonable for severe psychological stresses to take extra. But how far down the line do you come? Just going out driving in Auckland traffic in the morning is stressful, so there have to be some common sense decisions about what's unusual or severe.”

**more...**



## **Tips for Getting Attention at A&E:**

*From Professor Holdaway at the July forum in Auckland:*

"It can be difficult. It's the time when one has to be forceful. State that I (or my partner, etc) have Addison's disease, under-active adrenal glands, they are very ill, they need immediate medical treatment, this is an emergency, they have to come in right now. If you are in a waiting room, say we need to see the doctor right now, we can't wait, there is going to be a crisis here, and that's just what you have to say.

If you yell and shriek a bit, sometimes that's counter-productive, but if you are absolutely firm, then people get the message pretty quickly."

## **UPDATE NUMBER 15, MARCH 2002**

**On the following pages, we include some more excerpts, edited by Professor Holdaway, NZAN's medical advisor, from the address he gave at the July 2001 meeting in Auckland, ...**



**From our Medical Advisor, Professor Ian Holdaway:**

**Qu1. Do people with Addison's ever need adrenaline in emergencies?**

In Addison's disease of autoimmune cause, the inner part of the adrenal gland, the medulla, is not usually affected to any major degree.

The medulla is only damaged in TB or other disorders which totally destroy all adrenal tissue. Even in this situation there is no need to replace adrenaline production because most adrenaline and its relative, noradrenaline, is made in the nerve endings of the sympathetic nervous system.

Very rarely, an extremely ill person in intensive care may be given noradrenaline to maintain their blood pressure, but Addisonian individuals are not more prone than others to need such treatment.

**Qu2. What can I do about muscle cramps? (*Topic raised at the NZAN meeting in July last year*)**

Muscle cramps, particularly spasms in leg muscles, are very common in the population in general, particularly as people get older. From a medical perspective, they are frustratingly difficult to treat, because the basic understanding of their cause is incomplete.

Low levels of sodium or potassium can both give rise to cramps, and this may be apparent on blood tests of sodium and potassium. If you have a low blood level of sodium or potassium, and you have a cramp, that clearly identifies the most likely cause.

But you may have a low total body sodium or low total body potassium level, yet the blood level can still be in the normal range, but the total distribution through all the cells and tissues is reduced. (If you do a special isotope measurement on your total body potassium or total body sodium they may be low.)

For people with Addison's, who get cramps, especially after exercise, it is possible that there is an abnormality of adrenal replacement, particularly with fludrocortisone dosage.

Salt depletion (low sodium) due to insufficient fludrocortisone, is a common cause of cramp in Addison's individuals. However, if the fludrocortisone is over-replaced, then low potassium can occur, and that can trigger cramps too.

Stretching exercises of the muscles that you find are prone to cramp, can be helpful, before bed, or 2-3 times during the day.

If cramps persist after checking blood sodium and potassium levels, and after reassessing the replacement doses of hydrocortisone and fludrocortisone, then a 300mg tablet of quinine at bedtime is an option to discuss with your doctor. It is a standard cramp therapy, which is usually effective. Its only major side effect is the occasional development of a low platelet count.

**TAPES STILL AVAILABLE**



Copies of the tapes of Professor Holdaway's complete presentation are still available for \$10 per set – including a photocopy of the slides, and a summary of the order of the topics. Contact: Kathryn, PO Box 101-631 NSMC, Auckland; phone 09 445 6427, fax 09 445 6428; or contact Jeanette.

**Professor Ian Holdaway's presentation at the Auckland meeting in July 2001 gave a context to many important issues that affect people with Addison's disease.**

**In this issue of Update, we include edited transcript of the following topics:**

- \* Some challenges with cortisol replacement and monitoring**
- \* Optimising Fludrocortisone (Florinef)**
- \* Addison's disease and bone density:**

### **Some challenges with cortisol replacement and monitoring:**

What's new with regard to treatment of Addison's disease over the past five years?

"The unfortunate answer is that there haven't been any major studies that have compared one way of treating Addison's with another," said Professor Holdaway.

"That's what we would all like to have, but I doubt if that sort of study is ever going to be done, because there are not really enough people with the disorder to statistically show that if you take prednisone in the morning compared with lunchtime, or dexamethasone at night versus hydrocortisone in the morning, for example, that one way or treatment is better than another.

"For most of you, it is still an individualized decision. Some people seem to do well with prednisone and some people do well with hydrocortisone, and some take a mixture.

"How do you feel on your replacement? If things aren't right, you might make a little change, or try something different."

One of the problems in mimicking adrenal replacement is that cortisol secretion is episodic. Prof Holdaway showed on a slide, the blood cortisol levels throughout the day for a non-Addisonian individual.

"There is a diurnal rhythm, with blood cortisol levels highish in the morning, falling down to low levels later in the afternoon and early night, and back up again in the early hours of the morning.

"It's not just a big splurge of cortisol in the day, or even two or three splurges - it's produced in little spikes that start about 4am, in response to surges of ACTH, which are themselves entrained to some extent by the brain 'clock'

near the pineal gland. Trying to imitate that beautifully modulated normal rhythm with tablets is pretty difficult.”



Prof Holdaway showed a graph of blood cortisol levels through the day for a person with Addison's disease taking hydrocortisone.

The two or three doses of hydrocortisone a day, give rise to two or three peaks (without the brief spikes that are in the profile from a non-Addisonian), falling down essentially to zero in between peaks, especially in the morning before the first cortisone dose of the day.

“That's not very much like what normally happens, so you might look at that and wonder, how am I managing? There are obviously mysteries in this that we do not entirely understand.

“At the peak phase you are probably overdosed, and at some other times you have got much more than you would normally have at that time of the day, but it doesn't seem to lead to over-dosage effects, presumably because it's balanced out by times when you are a bit on the low side. But on the other hand, that might mean that you feel well when the cortisol is high and awful when it's low.

“It's possible that when cortisol levels are really low you might feel unwell, but what is not shown on this slide is what happens when the cortisol acts on the cells. Cortisol affects many body cells to keep our sugar and energy levels up, regulate stress responses, and many other actions.

“For cortisol, the half-life in the blood [the time that it takes to fall by 50%] is actually very short, just a few hours. But the enzymes and other chemicals that are regulated and made to work by cortisol, have much longer half lives than cortisol itself.

“In other words, the half life of the cell effect of cortisol is much longer than the half life of cortisol in the blood. So people with Addison's can get away with just taking cortisone 2-3 times a day, and remain well, because the cellular effects keep going even when the blood levels are low.”



Prof Holdaway illustrated that point with an example. “A patient of mine, on cortisone because of a pituitary problem, takes a biggish dose of hydrocortisone (35mg) as a single dose in the morning. That's all he has ever done, for many years.

“He gets up at 4am in the morning, and takes his hydrocortisone [and his thyroxine for hypothyroidism – because he has secondary adrenal insufficiency, he doesn't need fludrocortisone]. He then runs in the hills for

three hours, and then he works a full day as a welder. After work he runs for a further 1½ hours. He recently did a 190km run in South Africa. That's one extreme.

"Yes, he has to take his hydrocortisone when he does his main training schedule, which is first thing in the morning, but as you can imagine if you measured his blood level of cortisol when he is doing his afternoon run, he has probably got no cortisol detectable in his blood at all (that's been tested and confirmed).

"In this case the effects on the cells of this big surge of cortisone in the morning is still lasting quite well through the day and enabling his muscles to work and his lungs to provide plenty of oxygen for a 1½ hour run later in the day. And similarly when he did his 190km run he must have had times churning along there when his blood cortisol was very low.

"So it is difficult to approve of this treatment schedule when it doesn't seem physiologic, and you think that this doesn't look a great way of replacing cortisol. However, it is obviously difficult to know how important the timing of tablets actually is.

"What about the symptoms of under-dosage and over-dosage with hydrocortisone or prednisone?

"Unfortunately, as you all know, these symptoms are often fairly vague. Do you feel a bit more tired, are you running out of steam at different times of the day? Any assessment of these symptoms is bedeviled by the fact that people without Addison's disease run out of steam later in the day and feel tired and sleepy, so it's very hard to judge whether this is just the person and, yes, their profile is they are always going to feel that way no matter what happens, or is it because they haven't got the dosage of their tablets right. So it's a judgment that you and your doctor have to go through.

"What about tests that will help guide the dose of cortisone?

"This is a difficult area, because when you look at what scientific papers there are on the matter, and everyone's experience in general in measuring these things, the ACTH from the pituitary, the amount of cortisol in the blood, and the amount of cortisol in the urine don't actually provide enormously helpful information.

"24hour urinary cortisol may be a bit more useful - that's where you collect urine for a whole 24 hours, send it to a laboratory and they measure the cortisol in the specimen. But again because of those spikes that we just saw, when blood levels are high you filter a lot more cortisol into the urine.

"So most people taking hydrocortisone replacement for Addison's disease often have a somewhat elevated urinary cortisol, and if you look at that and think 'that looks a bit high', and reduce the dose, you can run into trouble with not enough cortisone replacement.

“Most of the cortisol in blood circulates bound to a protein – it’s only the unbound bit that gets into the cells to do its job, and it’s only the unbound bit that spills over into the urine where it can be measured.

“A person with Addison’s taking hydrocortisone would spill out a lot of cortisol into the urine when the blood levels are at their peak, and it would look as if they have too much cortisol in their system, but it’s because of the way the medication is being taken, and isn’t of itself a problem.

“So it’s a trial and error situation. Some people, such as the runner I mentioned, seem to manage on a single biggish daily dose of cortisol. But fiddling with the doses is not unreasonable for those who are not feeling very well throughout the day. Rather than pushing the total dose up, spreading it more over the day might be worthwhile, trying to more closely imitate the normal pattern.”

**Whilst the target is indeed optimal replacement of cortisol, that is often an elusive ideal.**

**“Most advisors are saying that probably our replacement doses are somewhat excessive. But countering that, there is very little evidence to show that usual cortisol replacement doses do any harm...**

**Which leaves most people with the feeling that it is better to err a little on the upper side, rather than on the lower side of replacement dosage.**

**However, the mineralocorticoid replacement is often underdone, and this can contribute to impaired day-to-day functioning, possibly even more than the cortisol replacement.”**

### **Optimising Fludrocortisone (Florinef):**

Prof Holdaway pointed out in his address at the Auckland meeting last July that in contrast to the situation where cortisol is often a little over-replaced, the mineralocorticoid aldosterone is often under-replaced.

Not having enough mineralocorticoid puts one at greater risk of an Addison’s crisis, and also can affect how well an Addisonian feels on a day to day basis.

The loss of aldosterone production may progress slowly over several years, so that an Addisonian’s need for fludrocortisone may start off low at diagnosis, but gradually increase.

“There’s a potential trap that individuals may feel a bit weak and tired, and so with their doctor they increase the hydrocortisone or prednisone part of their replacement, but that doesn’t really fix the problem.

The person either puts up with that level of unwellness, or the glucocorticoid dose is increased a bit more. These people may not be receiving fludrocortisone, or may be taking an inadequate dose.

“If you measure a blood renin level (the hormone that signals mineralocorticoid requirement), and the result is really high, that means the kidneys are crying out for more mineralocorticoid. So the correct thing isn't to increase the cortisone, it's to give a bit more fludrocortisone.”

“The renin level in the blood is quite a good marker, it stays at pretty much the same level during the day, and is not used enough by doctors and endocrinologists to get a feel for how much fludrocortisone individuals with Addison's disease need”.

(The blood for renin measurement can be taken at any medical laboratory, and is sent to a major hospital for analysis. The collection laboratory needs to check the blood handling and processing requirements.)



“You can also judge the appropriateness of the fludrocortisone dose by the levels of sodium and potassium in the blood. If you haven't got the dose right, those might be altered and the blood test from your doctor will show that. But it is a very crude guide. If they are abnormal then something is really not right at all, whereas you could still not be on enough fludrocortisone and blood sodium and potassium could be normal.

“Another way of judging fludrocortisone is by measuring your blood pressure. Your doctor should be doing your blood pressure test lying and standing, because if you are not retaining enough fluid with the fludrocortisone, you will get a low blood volume and feel a bit woosy and faint on standing.

“So if your blood pressure falls quite dramatically when you stand up then you're not on enough fludrocortisone. A fall of systolic (upper limit) blood pressure of more than 10-14 mm of mercury on standing should alert the doctor to this possibility.

**See box following...**

**“An average replacement dose of fludrocortisone is 0.1- 0.2mg per day.**

**Many Addison's individuals are on insufficient mineralocorticoid - the correct dose is established by lying and standing blood pressure measurements, and blood sodium, potassium and renin assessments.**

**Making sure the mineralocorticoid dose is sufficient is important to avoid having to increase the glucocorticoid dose to cover symptoms of mineralocorticoid deficiency.**

**This is especially important in those taking prednisone as their glucocorticoid, since this medication has no mineralocorticoid properties, by comparison with hydrocortisone or cortisone acetate which have partial mineralocorticoid effectiveness (20mg hydrocortisone provides the equivalent of about 0.05mg fludrocortisone.)”**

“Fludrocortisone has a relatively long half life in the body, so it isn't usually necessary to take it more often than once a day. However, as with glucocorticoid replacement, tablets are trying to mimic finely a modulated glandular response, and it isn't possible to get it perfect.

“The correct dose of mineralocorticoid also depends on the climate one lives in. Addisonians need to be alert when travelling to a hotter climate, for example on holiday. Since more perspiration means more loss of sodium and fluid, and hence possible sudden weakness, faintness, and tendency to Addisonian crisis can occur, especially if there is added stress as well.

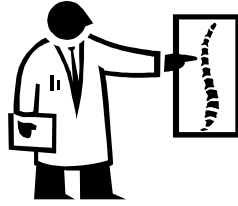
“Extra fludrocortisone (1/2-1 tablet) can be taken in anticipation, but as it can't kick in for a few hours, the short-term fix is salt – and plenty of fluids to minimise the extra risks due to dehydration.”

Professor Holdaway gave the example: “If you are walking around in Singapore and began to feel a bit faint, it's better to have a salty drink or some food with salt on it or a salt tablet, rather than waiting until the next day and increasing the fludrocortisone. That's going to have a much slower effect.

“Care is needed if the fludrocortisone dosage is increased too much, since this can cause fluid retention, increase blood pressure excessively, and lower the blood potassium level. Changes are thus best done with your doctor's guidance.

“If extra potassium is needed, it can come from more fruit such as bananas, or from Slow K (Slow Potassium) tablets. This can be one slight downside of pushing fludrocortisone too much. Extra potassium is indicated if the blood level is less than 3.5mmol/L”

## Addison's disease and bone density:



What about the risk of osteoporosis for Addisonians?

Osteoporosis is a condition in which there is a slow loss of bone mass. The reduction in bone strength increases the fracture risk. "It's painless until you break something."

"So are people with Addison's disease liable to get this problem? I think the good news is that overall, most people with Addison's disease have normal bones."

"There is, perhaps, a slight tendency to have lower bone density and sometimes osteoporosis, particularly if people have for one reason or another been on a reasonably high dose of corticosteroids, or if the disorder has gone on a long time, or in particular if they have other risk factors."

"For instance, a strong family history of fracture increases your risk of osteoporosis, and people who have already had broken bones or fractures might well have a higher risk of having osteoporosis, especially if they have a low calcium intake."

"There has been a study of bone density in Addison's which many of you would know about, done by Dr G Braatvedt from Auckland as principal author, with the help of many people with Addison's disease in New Zealand. In general, most individuals had bone density close to normal."

Prof Holdaway recommends having bone density checked, particularly women with Addison's disease. "Because of the bone protecting effects of estrogen, that's a consideration for using HRT after the menopause, although it's always an individual decision. The risk of reduced bone density in the Braatvedt study was related to the duration of the Addison's."

Professor Holdaway has written a concise article "Bone densitometry, a patient's guide", which outlines the measurement of bone density, and some treatments that are available. It can be accessed on the Karori Medical Centre website: [www.kmc.co.nz](http://www.kmc.co.nz). In 'health topics', select 'bones and joints', and then the bone densitometry article.

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## UPDATE NUMBER 16, JULY 2002

### **Comment from NZAN's medical advisor, Professor Ian Holdaway:**

Reduction of corticosteroids should be gradual, 2.5-5mg hydrocortisone or 0.5-1mg prednisone each 1-2 weeks, with careful monitoring of symptoms and, if possible, blood pressure. Symptoms of tiredness, lethargy, extreme irritability, and muscle aches, are a warning that you're cutting down a bit fast. If you are dizzy or have a BP lower than 100mm systolic (the upper number in the blood pressure reading), this may indicate not enough corticosteroid or fludrocortisone.

### **Comment from Professor Holdaway:**

1. The appropriate use of injected hydrocortisone needs to be constantly emphasized – but as mentioned by the writer, people naturally forget about this when a major illness or crisis hits them. Sometimes a partner or relative is the best person to remember and initiate this.

2. People with Addison's disease need to be assertive and proactive to get appropriate care.

If patients are having difficulty getting Addison's medications on time in a hospital ward, and especially if they are not in a medical ward (eg they are in surgery, othopaedics, eyes/ENT, gynaecology etc), they or their relatives should demand firmly that the medical registrar on call, and the endocrinologist on call, should review their case immediately. If necessary shout – it is amazing what a loud voice can achieve!

Not giving regular steroids to an Addisonian patient (plus a supplement if the individual is ill) is unforgivable. Many hospitals will permit self-medication, and the patient should ask the Doctors and/or the Pharmacist about this. Pharmacists are often attached to hospital "teams", but can also be asked for specifically, usually via the Charge Nurse on the ward.

## **Question: Is Solu-Cortef relevant for people with Secondary Adrenal insufficiency?**

People with primary and secondary adrenal insufficiency are essentially in the same boat, both needing a replacement glucocorticoid medication. But Shirley, one of our treated Cushings members, wonders how relevant some of the material in the newsletters is for her. In particular, is having injectable hydrocortisone on-hand for emergencies, and understanding when and how to use it, important for people who have secondary adrenal insufficiency due to hypopituitarism?

### **Answer: from NZAN's Medical Advisor, Prof Holdaway:**

Yes, individuals with secondary adrenal insufficiency may on occasions need injected hydrocortisone similar to those with Addison's disease. This occurs less often with secondary adrenal deficiency because these individuals still have normal levels of aldosterone and do not have the same risk of low blood pressure and collapse when they cannot take or absorb their replacement treatment. Nonetheless, those with severe illness, accident or stress still need an increase in replacement steroid, and if the person is vomiting or unconscious this must be given by injection.

Whether an individual with secondary adrenal insufficiency needs to have injectable hydrocortisone available is an individual decision, usually best made in consultation with their GP or endocrinologist. All Addison's individuals are strongly encouraged to have injectable hydrocortisone (Solu-Cortef) on hand.

### **Comment from Professor Holdaway on DHEA and HRT**

The dose of DHEA differs somewhat in New Zealand compared with overseas countries. The formal studies of DHEA in Addison's have usually used a micronised DHEA preparation that seems to be less well absorbed than the local preparation of DHEA made in New Zealand by Pharmaceutical Compounding in Birkenhead, Auckland. Whereas the overseas studies used doses of 25-50mg DHEA daily, the NZ preparation seems to be better absorbed, and doses of around 10mg daily may be all that is needed. I generally start people on 10mg, and then measure the blood DHEAS level (the sulphated form of DHEA), 2-4 hours after a dose, to check that it is not too high. Using the full 25-50mg dose locally may lead to acne, increased hair growth, and other side effects.

The use of Hormone Replacement Treatment will have to be reassessed for individual women in the light of the recent findings of the Women's Health Initiative study in the US, and will be a topic in a future newsletter. Short term use of HRT remains a safe option to relieve difficult menopausal symptoms. If individuals decide to stop HRT, remember that you may need slightly higher doses of hydrocortisone once estrogen replacement ceases, perhaps up to an extra 5mg hydrocortisone per day.