

Assessing the Potential for Fine-tuning the Management of Addison's Disease/Steroid Replacement Therapy

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1. Introduction

Addison's Disease is a rare chronic condition due to the destruction of the adrenal cortex. Symptoms of the disease once advanced can include skin pigmentation, weight loss, faintness, nausea, diarrhoea and fatigue. Continuous treatment with steroid replacement therapy is required, which aims to simulate as closely as possible the requisite amounts of cortisol and aldosterone that the patient can no longer adequately produce. Stressful change, typified by trauma, illness or injury, can produce an Addisonian crisis unless suitable treatment is administered.

The Addison's Disease Self Help Group in the UK was founded by Mrs Deana Kenward twelve years ago and membership has grown to 350 in 1996.

This research was initiated, conducted and analysed by a member of the group. It was prompted by the observation of a number of recurring problems raised in the bi-monthly newsletters which suggested that certain post-diagnosis symptoms, some minor, some not, could be quite widespread amongst patients being treated for Addison's Disease.

The fact that these are often non-specific in combination with the rarity of the disease makes some of these problems unlikely to be noticed much or to seem valid if, indeed, raised at all by the patient in a clinical setting. As would be expected, a fairly broad spectrum of opinion is encountered amongst medical specialists on dosage levels and whether or not particular side-effects exist as a result of the disease, the treatment or a combination of both. A practical disadvantage of divergent views from the patient's perspective is that potentially relevant problems can be pushed underground.

Within the supportive climate of the newsletter and the group itself, however, these issues become more visible and there seemed to be an opportunity to develop a "collective voice" in this respect using the membership database that Deana Kenward has created to generate a national survey of patients with Addison's Disease.

Perhaps one of the key questions is the extent to which baseline levels of steroid treatment can be precisely defined. What is the effect (if any), for instance, of three or four decades of a few mgs daily surplus of hydrocortisone? If the symptoms often described by group members are traceable in some way to the disease and /or the treatment, then extrapolating the cause and effect may do much to improve the quality of life for those with Addison's Disease, bearing in mind that even a minor adjustment can have a major impact.

It is hoped, therefore, that the results of this research will facilitate some fine-tuning of the management of the disease via steroid replacement therapy.

2. Objectives

The objectives of the study were as follows:

- (i) To assess the nature and degree of post-diagnosis symptoms.

- (ii) If significant patterns should emerge, to have these symptoms acknowledged and validated by medical professionals, raising awareness of them amongst both specialists and GP's.
- (iii) To prompt a clinical study of why these symptoms occur and to have issued a set of comprehensive guidelines on what, if any, preventive or ameliorative measures can be practicably taken.

3. Methodology

A short postal survey comprising both open and prompted questions distributed to 350 members of the Addison's Disease Self Help Group during June 1996.

The results were analysed using basic quantitative techniques involving percentage response analysis.

4. Sample

Of the 350 questionnaires that were sent out, 157 were returned for analysis, representing a 45% response rate. Of these, 7 contained insufficient data for analysis.

The following findings, therefore, are based on a total sample of 150.

The majority of group members are resident in the UK. A handful of responses came from members who live overseas.

5. Profile of Respondents

SEX		
	no.	%
Male	30	20
Female	120	80

This strong female bias is reflected in the group membership as a whole, as well as in the incidence of Addison's Disease.

AGE		
	no.	%
<20	3	2
21-30	11	7
31-40	29	19
41-50	35	23
51-60	39	27
>60	33	22

AGE & SEX						
	male			female		
	no.	% male	% total	no.	% male	% total
<20	3	10	2	0	0	0
21-30	2	7	1	9	8	6
31-40	6	20	4	23	19	15
41-50	5	17	3	30	25	20
51-60	10	33	7	29	24	19
>60	4	13	3	29	24	19

6. Findings

(i) Medication

TYPES (only those used to control the symptoms of Addison's Disease have been included here).

	no.	%
(i) Hydrocortisone	134	89
Prednisone	10	6
Cortisone Acetate	7	5

(ii) Fludrocortisone	no.	%
Take Fludrocortisone	128	85
Do not take Fludrocortisone	23	15

Frequency of Dosage

(i) Hydrocortisone (or equivalent)	no.	%
Twice daily	108	72
Three times daily	34	23
Four times daily	2	1
Other daily	6	4

Nearly three-quarters of the total sample take hydrocortisone or equivalent, therefore, on a twice daily basis, with the majority of these taking the medication early in the morning, on rising or with breakfast and then again in the late afternoon.

Timing of Dosage

Chart I: Hydrocortisone

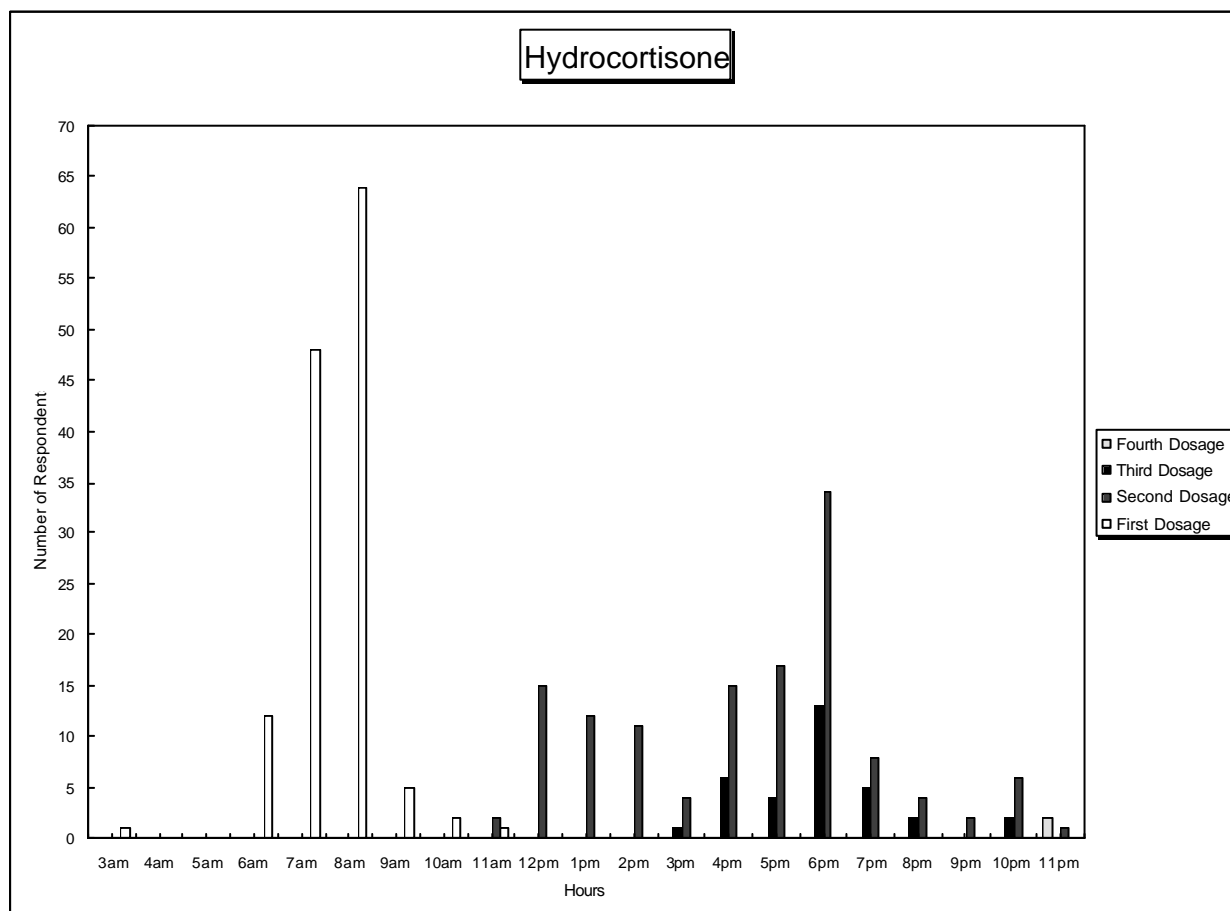


Chart 2: Prednisone

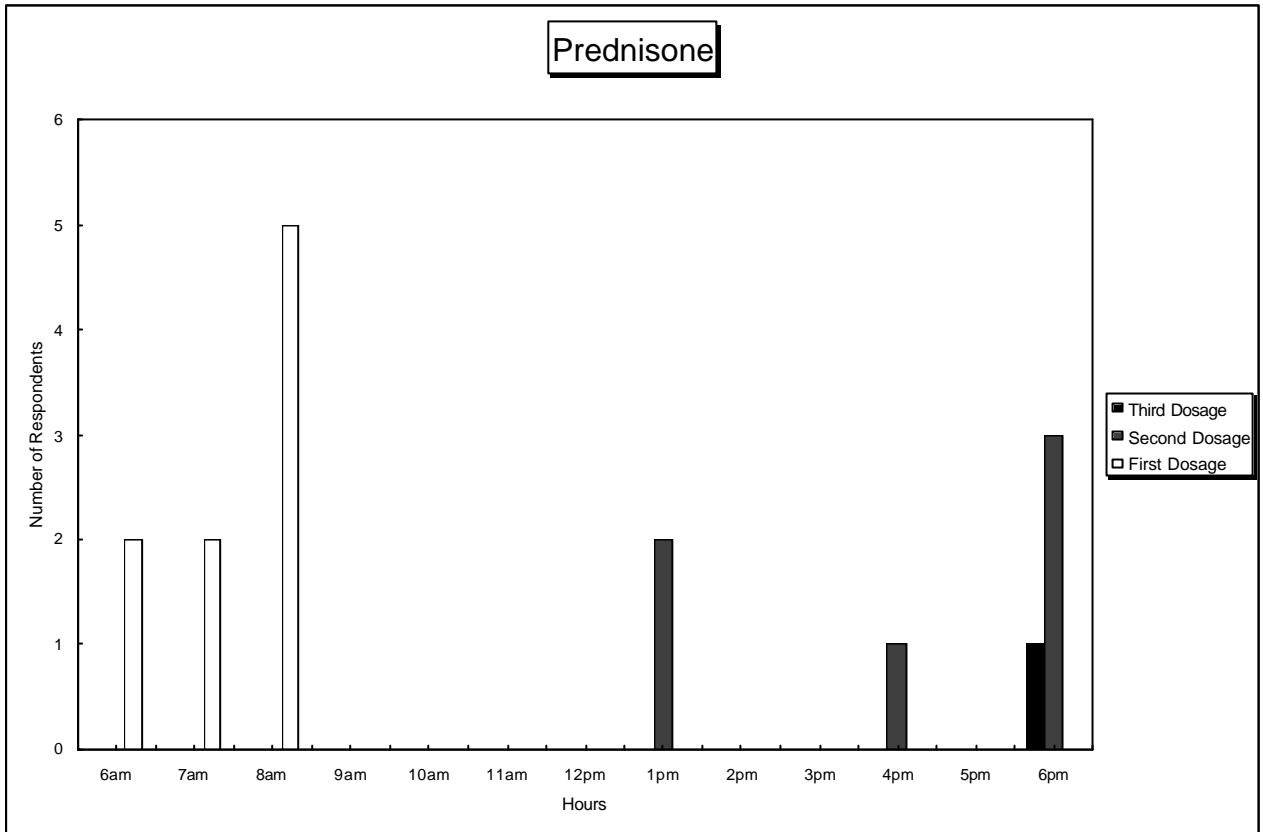
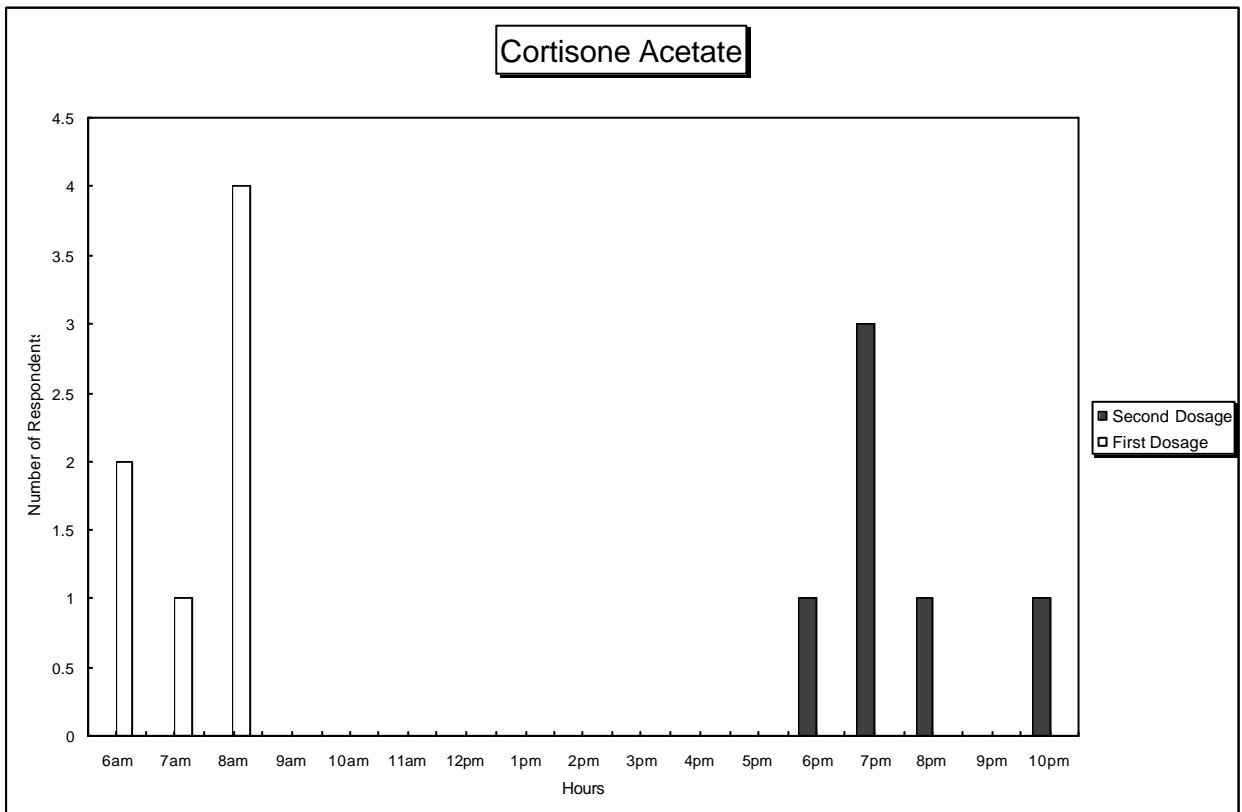


Chart 3: Cortisone



Fludrocortisone

64% of respondents who take fludrocortisone take 100mcg daily, most often with the first or morning dose of hydrocortisone or equivalent.

21% take 50mcg daily or 100mcg on alternate days.

6% take 200mcg daily.

Other variants (2 or less respondents) ranged from 25mcg every other day to 200mcg twice daily.

(ii) Dosage Relative to Weight

Whilst not the sole criterion, weight is a principle determining factor in establishing baseline levels. Correct dosage levels are also contingent on individual metabolic rates and other medical factors.

The most sophisticated technique for assessing dosage is a hydrocortisone day curve analysis.

Of the 150 respondents, three referred to having had such an analysis and a further respondent is awaiting one. Two of the three had their dosage substantially reduced following the results. Existing dosage was confirmed as being accurate for the third, but the timing of the dosage was adjusted. Each recipient records considerable improvement in their condition: two through weight/excess fluid loss; the third, via the elimination of frequent bouts of hypoglycaemia. A sample of three, however, is insufficient to suggest any particular trends.

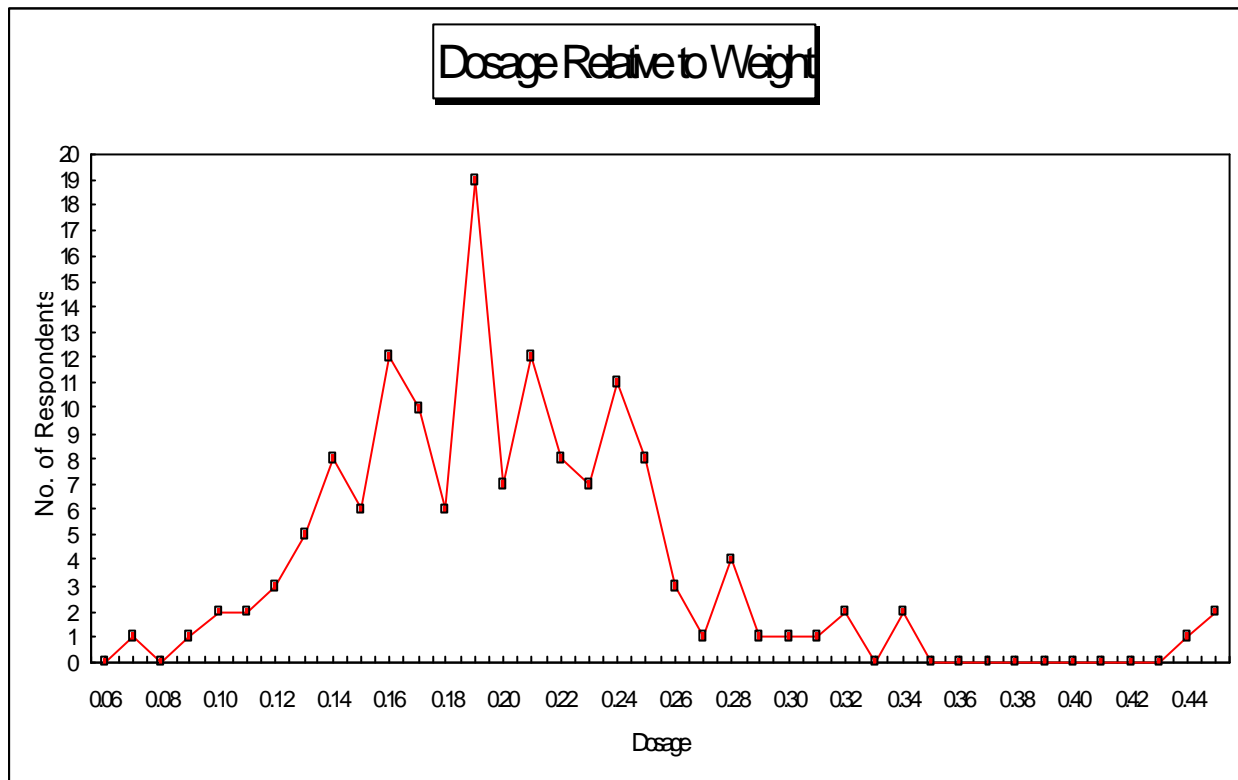
Nevertheless, using the total sample, a weight/dosage ratio is readily measured and the following chart is potentially valuable as a preliminary comparative guide.

The calculations are based on mgs/hydrocortisone per lb of body weight with the following conversion: 25mg cortisone acetate = 20mg hydrocortisone = 5mg prednisone.

A worked calculation is as follows:

Body weight = 8st 4lbs; daily dosage = 20mg hydrocortisone = 20mg = 1161bs = 0.17

Chart 4



Total respondents = 149 (excludes one respondent whose dosage is unusually high due to steroids conflicting with other medication).

As the chart demonstrates, most respondents are well within the curve, the most common dosage per lb body weight being 0.19.

There are evident disparities, however, and the data suggests that those well out with the boundaries of the curve might benefit from a day curve analysis if one has not already been conducted.

(iii) Weight Gain

Excessive weight gain and difficulty in controlling weight are recurrent problems cited by Group members. There is a perception amongst participants that steroids increase the appetite and that following the usually quite rapid return to a normal body weight once treatment commences, it is alarmingly easy to acquire extra pounds.

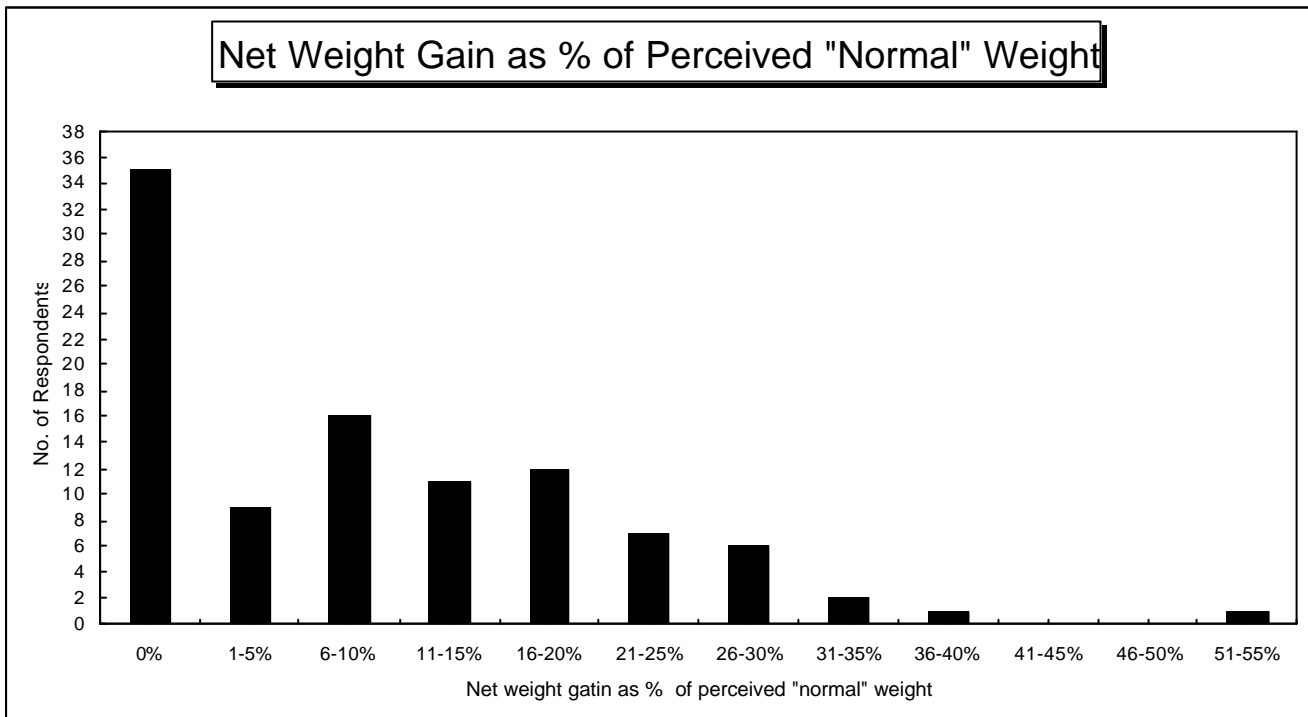
The following chart demonstrates a definite propensity to weight gain over and above perceived "normal" (as opposed to "ideal") weight, with 55% of respondents claiming additional weight gain in excess of 5% and 40% claiming gains of more than 10%.

The overall results should be read in the context of a general tendency to put on some weight as one grows older and does not include such variables as a change in exercise habits etc.

However, if the rationale is that precise replacement therapy should not lead to surplus weight gain, then the results suggest that some respondents may be on dosages in excess of their actual needs.

The sample here is 99, being the total number where a net gain or no net gain was definitely calculable. It excludes all those who reported a gain but where it was unclear whether the increase included the recovery of weight loss prior to diagnosis. It also excludes any respondent whose additional medical circumstances could also contribute to weight gain or loss.

Chart 5



(iv) Post-Diagnosis Symptoms

Prompted

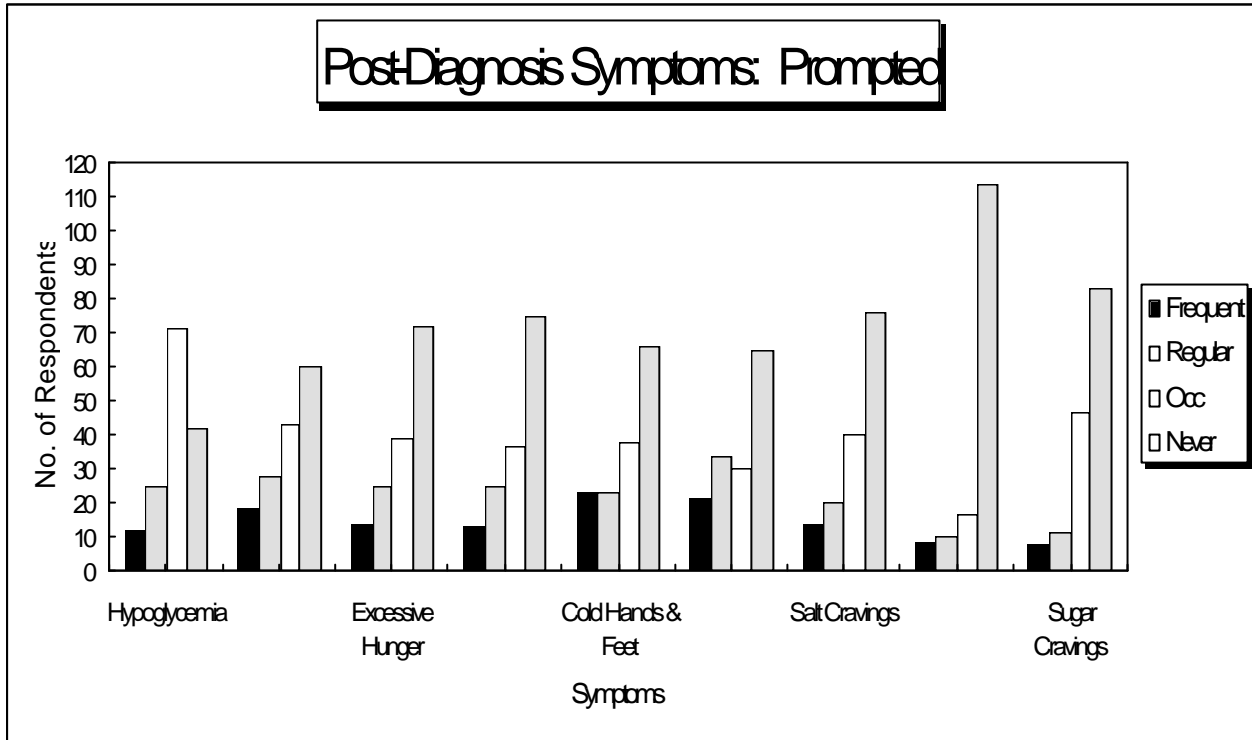
The symptoms listed on the questionnaire comprised those commonly described by Group members and the grid was used to establish the extent and degree to which they occurred.

The results show that a substantial minority are subject to these post-diagnosis symptoms either regularly or frequently, the most prevalent being excessively dry skin, cold hands/feet and excessive thirst. At least half the sample experience some of these symptoms occasionally or more.

Whilst many of these problems may seem trivial, they can cause considerable discomfort and have, therefore, a certain validity. It would be useful to understand the physiological causes of these complaints and establish whether any of them could be better controlled or indeed prevented, particularly in the case of hypoglycaemia, being potentially the most significant.

It should also be noted that liquorice cravings, whilst a regular/frequent problem confined to 13% of respondents, should not be underestimated since liquorice is an adrenal stimulant and those who experience cravings seem to do so very severely, one respondent actually requiring hospitalisation following an uncontrollable bout of liquorice consumption.

Chart 6



(v) Post-Diagnosis Symptoms

Spontaneous

Two open-ended questions were included at different stages in the survey. These were:

- (i) "Have you had any related changes/problems since you were diagnosed?"
- (ii) " Are there any activities/aspects of your life that Addison's Disease has particularly affected?"

Additionally, an "other" category was included in the prompted symptoms question.

During the analysis of the results, a pattern of spontaneously cited problems emerged in response to one or other of these questions.

It made sense to amalgamate these responses, de-duplicating where applicable and to categorise these loosely according to general type. The categories are not meant to be mutually exclusive or definitive in a medical sense: they are an aid to the presentation of what seemed to be demonstrable patterns, whilst allowing for individual expressions of similar or synonymous complaints.

The first open-ended question about related changes/problems was originally designed to gauge the extent to which other medical conditions occasionally associated with Addison's Disease were prevalent.

These are listed below, together with other specific medical conditions which did not readily belong in any of the groupings that follow:

	no.	%
Diabetes	8	5
Hypothyroidism	25	17
Hypoparathyroidism	1	*
Hyperthyroidism	1	*
Cushing's Syndrome	1	*
Hyperlipidaemia	3	2
M.E.	3	2
Asthma	6	4
Thrush	4	3
High Blood Pressure	6	4

Group 1: Weight gain/fluid retention variously described as:	no.	%
Swelling legs/feet	2	1
General weight control	9	6
Moon face/bloating	5	3
Fluid retention	8	5
	24	15

NE: see also Findings: weight gain in this context

Group 2: Emotional/hormonal variously described as:	no.	%
Depression/mood swings	23	15
More affected by stress	7	5
Reduced/lost libido	8	5
Improved libido	1	*
	39	25
(female only)		
Increased PMT	7	6
Amenhorrea/irregular periods	3	2
Early menopause/no children	2	1
	12	9
(male sample only)		
Breast area enlargement	1	3

Group 3: Circulatory variously described as	no.	%
Pins and needles/tingling	4	3
Severe sweating	3	2
Extreme sensitivity to cold/heat	16	11
Raynauld's Disease	2	1
Hot flushes (not menopausal)	2	1
	27	18

NB: See also "Prompted symptoms: Excessively cold hands/feet" in this context.

Group 4: Dermatological variously described as:	no.	%
spots/acne	4	3
red face	2	1
rosacea	1	*
excess body/facial hair	2	1
hair loss	5	3
bruising (easy or dappled)	10	7
pigmentation	9	6
thinning skin	7	5
ulcerated legs	2	*
splitting nails/skin	3	2
	44	28

NB: See also Prompted symptoms: "Excessively dry skin" in this context.

Group 5: Orthopaedic variously described as	no.	%
bone thinning/osteoporosis	10	7
muscle pain	9	6
muscle weakness/wastage	10	7
joint pain	7	5
arthritis	3	2
osteomyelitis	1	*
discoid lupus	1	*
chondromalacia	1	*
cramp	4	3
	46	30

:

Group 6: Gastrointestinal variously described as:	no.	%
ulcers	3	2
heartburn	4	3
stomach pain	1	*
general stomach problems	5	3
chronic constipation	1	*
diarrhoea	2	*
nausea	2	1
	18	9

Group 7: Addisonian symptoms variously described as:	no.	%
Lack of energy/fatigue	58	39
Dizziness/faintness	5	3
Breathlessness	4	2
Poor sense of balance	3	2
Pernicious anaemia	1	*
	71	46

Group 8: Social/financial variously described as:	no.	%
Loss of self/social confidence	7	5
Nervous travelling overseas	10	7
Can't work or work fulltime (due to Addison's)	5	3
Unable to get mortgage protection	1	*
Loss of education (due to Addison's)	1	*
	24	15

Other non-specific symptoms, variously described as:	no.	%
Insomnia/sleeping difficulties	10	7
Migraine/headaches	6	4
Poor memory/concentration	13	9
Noticeable longer to heal/recover from injury/illness	4	3
Bitter taste in mouth	2	1
Mouth ulcers	2	1

It is not within the remit of this study to assess the medical nature of these problems, but it is hoped that the prevalence with which some are spontaneously mentioned suggests that they are worthy of serious clinical consideration. Perhaps most notably, 20% of all respondents refer to depression and the effects of stress, 17% describe a variety of circulatory ailments, 28% dermatological disorders, 30% orthopaedic problems (7% of these citing osteoporosis) and as many as 39% expressing persistent lethargy/lack of stamina, the "need to pace one's self carefully".

Obviously having Addison's Disease will not preclude the onset of other conditions and the frequency with which some of these apparently occur needs to be judged against the average likelihood of developing a particular complaint. But it is worth pointing out that there is an awareness amongst respondents of the ease with which difficulties can be blamed on Addison's Disease and the general tenor of replies reveals a definite caution in doing so. These figures reflect that caution. There is also sufficient anecdotal evidence to suggest that respondents are by and large pragmatic about their condition. Nevertheless, whilst it is quite feasible to live with many of these symptoms, some are painful, debilitating, distressing and in the case of osteoporosis, potentially life threatening. Therefore, any reduction or, indeed, prevention would have a significant positive impact.

(vi) Self Help Strategies:

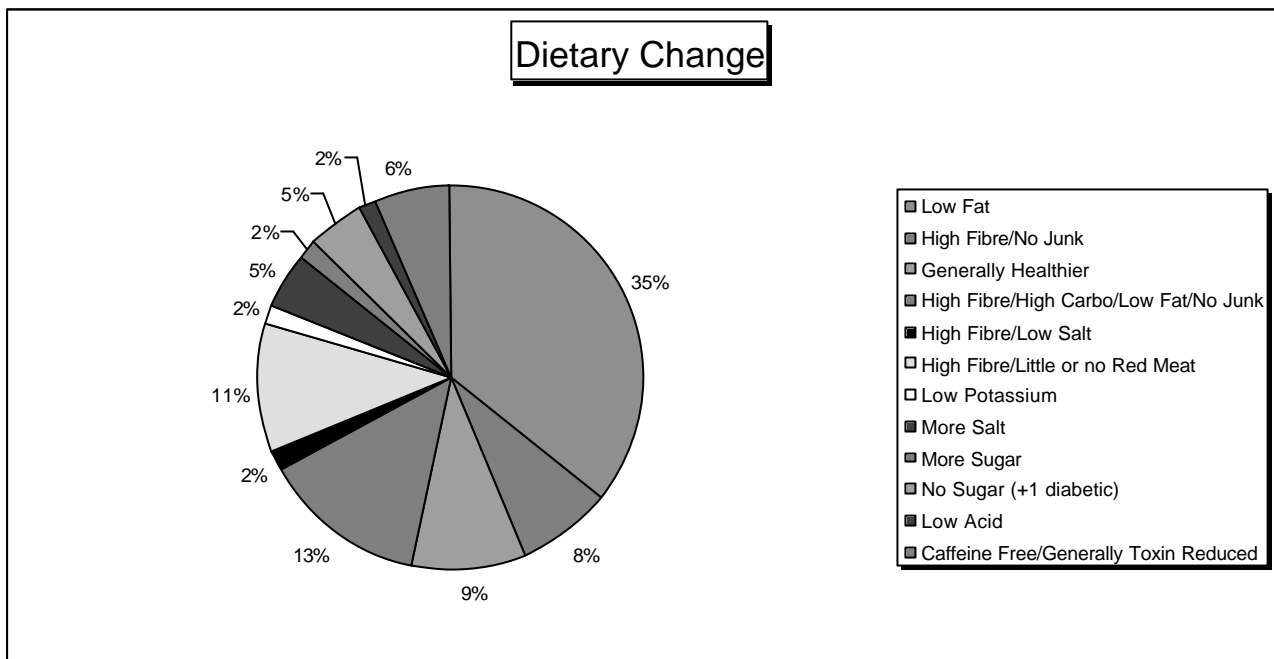
Diet/Exercise/Supplements

(i) Diet

When asked if dietary changes had been made post-diagnosis, 56% of respondents said they had not altered their eating habits, whilst 44% said they had.

Amongst the latter group, the general trend was towards healthier eating patterns, although dominated by apparent efforts to lose weight: 34% of those who had made dietary changes follow a low fat diet.

Chart 7



The rest is rather a mixed picture, sometimes even contradictory (low salt vs more salt). The results as a whole suggest that in depth nutritional advice might be beneficial, to ensure, for instance, that a low fat regime does not undermine calcium intake and overall to assess whether steroid treatment and/or Addison's has any effect on the physiological processing of foods.

(ii) Exercise

	no.	%
Exercise	87	55
Do not exercise regularly	67	45

More than half of all respondents exercise regularly in a variety of ways. There is a low level of awareness of weight bearing exercise being potentially beneficial in helping to maintain bone density and muscle strength. Equally, there is some confusion as to whether an increase in hydrocortisone is advisable before undertaking strenuous exercise.

Some respondents feel more able to undertake exercise following diagnosis; conversely, others feel less able or unable to exercise at all.

(iii) Vitamin/Mineral Supplements

41% of all respondents supplement their diet with extra vitamins or minerals, 18% of these on the advice of a doctor or specialist.

The rest relied on their own judgement and/or that of a pharmacist or health food shop or book.

The five supplements most frequently used are:

	no.	%
Cod liver oil	25	41
Calcium	20	32
Multivitamins	15	24
Vitamin B/B Complex/B 6	15	24
Vitamin C	13	21

Other types of vitamins/minerals with two or more mentions were:

	no.	%
Garlic	7	11
Evening Primrose Oil	7	11
Iron/ferrous sulphate/black strap molasses	4	6

It seems clear that a relatively high proportion of respondents feel that supplementary vitamins or minerals may be protective or beneficial, but it remains a somewhat hit or miss strategy, with little professional input.

The question arises as to the value of supplements per se (assuming an adequate diet) and whether the use of steroids even at replacement dosage levels counteract the effects of vitamins and minerals and so increase the amounts needed by patients with Addison's Disease. An assessment of what, if any, combinations of nutrients can be used to best effect to maintain a healthy immune system and at what sort of dosage levels could, therefore, be helpful.

(vii) Specialist Help

77% referred to medical problems which they perceived as being related to Addison's. Of these 97% raised them with either their GP or specialist.

Of the sample who discussed difficulties with their GP or specialist, 35% believed they had received constructive help. This ranged from general support to the arrangement of bone density scans, dosage adjustment, advice on salt intake and the prescription of anti-depressants or sleeping tablets in addition to the diagnosis of conditions such as hypothyroidism.

The more non-specific complaints were much less likely to be mentioned in a clinical setting.

From one perspective, the tendency to regard some of the problems described as invalid is understandable. Addison's Disease patients are a rarity and samples of one or two referring to cravings, weight gain etc. may not be very credible.

However, this data suggests that a variety of post-diagnosis symptoms are commonly experienced and that at least some of these may be due either to the disease itself or the treatment or a combination of both.

When asked in the questionnaire what else they would like to know about the disease, patients wanted much more information on long term use of steroids, especially in relation to osteoporosis which is perceived as a very real threat, pregnancy and Addison's, and emergency procedures/crisis management. In this respect, some are instructed to self-inject under certain circumstances; some are not and there is a general concern that even during hospitalisation, the dosage increases necessary to combat illness, trauma or surgery are deemed to be very arbitrarily judged. It is therefore little wonder that some respondents spontaneously referred to their own caution about travelling abroad.

7 Summary of Findings

(i) Medication and Dosage

The vast majority of respondents use the same combination of medication, namely hydrocortisone and fludrocortisone. The frequency and timing of dosage is somewhat variable, through three-quarters take hydrocortisone on a twice daily basis. There is a significant variation in the amount of fludrocortisone taken, though the average was confirmed as 100mcg daily. Weight/ dosage ratios suggest that, whilst a consistent pattern emerges, respondents at either end of the spectrum may not be on an optimal baseline dosage of hydrocortisone. Only three respondents referred to having had a hydrocortisone day curve analysis.

(ii) Weight Gain

More than half of all respondents felt they had exceeded their "normal" body weight (i.e. pre-emaciation) by more than 5%; nearly 40% felt they had exceeded this by more than 10%. Surplus weight gain post-diagnosis appears to be a very real problem.

(iii) Post-diagnosis Symptoms

When prompted, a significant number of respondents (13-37%) confirmed that they experience one or more of a variety of post-diagnosis symptoms either regularly or frequently. By and large, half the sample experience some of these symptoms at least occasionally. Exceptions to this are liquorice and sugar cravings which are more unusual. However, those who do suffer from liquorice cravings appear to find them very difficult to control.

On a spontaneous level, a variety of similar sounding symptoms were described, the most notable being 15% mentioning weight gain/fluid retention characteristics; 37% describing emotional/hormonal imbalances; 17% referring to circulatory problems (in addition to the prompted "cold hands/feet"); 28% citing dermatological symptoms (in addition to the prompted "dry skin"); 30% described orthopaedic problems and 46% classic Addisonian symptoms, especially persistent lack of energy/fatigue.

(iv) Self-Help Strategies

More than half of all respondents have made dietary changes since diagnosis, mostly in favour of a low fat regime which probably reflects concern about weight gain/control. A similar number exercise on a regular basis and 41% supplement their diets with extra vitamins and/or minerals. Dietary and supplement choices are mostly based on personal judgement and the range of responses confirms the somewhat piecemeal and arbitrary nature of these self-help approaches, given the general lack of professional input.

(v) Specialist Help

About a third of all respondents felt they had received a constructive response from their GP or specialist in relation to a particular problem. More non-specific symptoms were rarely raised during check-ups. This does suggest, that there is considerable scope for strengthening the interface between doctor and patient, particularly given the heavy dependency on self-management on a day to day basis.

8. CONCLUSIONS

There is considerable evidence from the data collected that certain post-diagnosis symptoms exist amongst patients with Addison's Disease and in some cases are widespread.

The question arises as to cause and effect and the degree to which this can be established in relation to each. If any links can be clinically established, are they due to inaccurate baselines, less than optimal dosage times, the disease per se or the treatment per se?

In any case there seems to be a clear opportunity to fine-tune hydrocortisone levels through greater use of day curve analyses. There also seems to be considerable potential to bridge a gap perpetrated on both sides between patient and doctor via exchange of more rather than less information.

Additionally, more professional advice on diet, nutrition and lifestyle may do much to improve the effectiveness of self-help strategies and reduce the trial and error basis on which these tend to be adopted.

9. Next Steps

- (i) to present these findings to medical specialists
- (ii) to prompt further debate on the issues raised
- (iii) to have the trends suggested by this study tested for clinical proof