Cushing's syndrome
Newell-Price J, Bertagna X, Grossman AB, Nieman LK
Lancet 2006;367:1605–17

This recent review in the Lancet seminar series will be useful for those preparing for examinations, as well as those participating in continuing professional development (CPD) schemes. It is an easy-to-follow article prepared from a literature search over the last five years and contains enough references (nearly 200 in total) to fulfill any requirement for more in-depth reading.

The review attempts to update the reader on the current understanding of the pathogenesis, clinical features and diagnostic strategies – the latter of most interest to clinical biochemists, who are acknowledged as key members of the diagnostic team.

What was of interest to me is the increasing recognition of the condition presenting with more subtle clinical and biochemical phenotypes amongst obese individuals with type 2 diabetes. Preliminary testing for hypercortisolaemia in this group has identified an incidence of between 2% and 5% which, if confirmed in further large-scale prospective studies, could pave the way for more widespread screening and yet more endocrine test requesting.

Little is known about the pathogenesis of the most common cause of Cushing's syndrome – corticotrope pituitary tumours. In contrast, more is known about the aetiology of the more rare causes of adrenal Cushing's syndrome in relation to the functioning of the corticotrophin receptor. The long-established clinical features are listed, with emphasis given to the incidence of psychiatric symptoms among 70% of cases at presentation, which are not completely resolved by treatment. Impaired short-term memory and cognition can persist for some time afterwards. The psychiatric symptoms have been associated with a reduction in apparent brain volume, which slowly reverses after correction of the hypercortisolaemia.

The diagnosis of floridly presenting Cushing's is easily made clinically with biochemical confirmation. The mainstay of the diagnosis relies on one of three tests: urinary free cortisol, the overnight or low-dose dexamethasone suppression test, and midnight plasma cortisol. With increasing involvement of primary care the overnight dexamethasone test has a lot of convenience for the patient but the more cumbersome 48-h low-dose suppression test is claimed to be more specific and easily performed – if not in primary care, at least in the outpatient setting. Low specificity has been cited as a limitation of the urinary free cortisol measurement, and this might be improved by the use of more specific non-immunoassay measurements such as tandem mass spectrometry. An algorithm is presented which details how the cause of Cushing's syndrome – pituitary, ectopic or adrenal – can be determined with heavy reliance on imaging and dynamic invasive testing undertaken at a referral centre.

Effect of enhanced feedback and brief educational reminder messages on laboratory test requesting in primary care: a cluster randomized trial
Thomas RE, Croal BL, Ramsay C, Eccles M, Grimshaw J
Lancet 2006;367:1990–6

Those of us who attended the National Audit meeting in Manchester in November 2005 were treated to a sneak preview of this research courtesy of one of the authors. We benefited from his entertaining presentation, lightened by references to well-recognized characters and colloquialisms from topical television comedy – notably, and with particular relevance, 'Computer Says No'. This was a timely study conceived by a chemical pathologist in the face of seemingly uncontrollable demand for laboratory testing. The workload from primary care has increased by 83% in the years 2000–04, the most notable contribution attributable to the new contract introduced for general practitioners in the UK in January 2004.

The study sought to determine the effect of educational intervention as a means of reducing inappropriate and excessive test requesting. It involved 85 general practices which were randomized in a controlled fashion to receive enhanced feedback on their requesting practices and/or educational information appended to pre-selected test results. The nine pre-selected tests included tumour markers (notoriously inappropriately used for the diagnosis and screening of malignancy), haematins, thyroid function tests and gonadotrophins. The primary outcome was the determination of whether this educational intervention had any effect on test requesting. This was achieved to some degree, with the practices who received either of the two types of feedback less likely to request the pre-selected tests. The combined effect of both types of intervention was equivalent to a reduction of 22% in the test requesting – notably thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH) and vitamin B12. Both detailed feedback of requesting activity and appended educational reminders appeared to be effective strategies for controlling demand. The study, while only 12
months in duration, was prompted by the encouraging
results of a study published a decade earlier where
the effect of intervention persisted over nine years.
The advent of computerized order communication
system with interactive real-time interrogation
should afford some measure of control over test
requesting in real time. This paper adds to the accumu-

lating body of recent research showing workable strate-
gies to control test requesting, both in the future and in
real time.

Helen Losty
Contributions to Journal Watch are invited from all readers and
should be sent to Helen Losty (e-mail: helen.losty@nhs.net)

Piscator

Piscator has been pedalling away somewhat
frantically in Poland these last few weeks – a
form of transport guaranteed to keep me con-
scious, given the pain in my posterior from saddle fati-
gue. Not so the insulin-dependent diabetic who runs
the risk of hypoglycaemic episodes while at the wheel,
with potentially fatal consequences. Enter man’s best
friend to save the day and the first report of the canine
detection of hypoglycaemic episodes while driving
(Diabetic Med 2006;23:335). The patient was an elderly
French farmer with a 20-year history of type 1 diabetes,
gave details of at least weekly hypoglycaemic epis-
odes of which he was mostly unaware but which were
detected by his trusty mutt Bergere. He would toil long
and hard in the fields all morning and it was when he
would be driving back to the farm house at lunchtime
that his dog would sit up in the back seat, stare and
then bark loudly and continuously until the farmer
stopped his vehicle. Measurement of his capillary blood
glucose would invariably demonstrate hypoglycaemia.
He had modest diabetic control, with glycylated hae-
moglobin A1c (HbA1c) ranging from 7.8% to 9.2%. The
farmer was grateful to his dog for over 17 years of vigi-
lance prior to the dog’s demise, at which point the farm-
er retired. This is not the first time that dogs have been
reported to demonstrate behavioural changes when
their owners have hypoglycaemia, and a previous case
identified by Piscator described the utility of this novel,
fully biocompatible, patient friendly alarm system for
the non-invasive detection of hypoglycaemia in the
home. The exact mechanism whereby dogs can detect
the development of hypoglycaemia is not unknown,
but possible theories include olfactory changes related
to sweating, detection of muscle tremor, and beha-
vioural alterations. Although essentially a feel good
story of All Creatures Great And Small, charitable orga-
nizations are investigating the use of trained dogs as
‘medical alerts’ for diabetic patients with hypoglycae-
mia unawareness.

Type 2 diabetes is multifactorial in origin, but as
a child reared on ‘spuds’ I have to take note of
the association between potato consumption
and the risk of type diabetes (Am J Clin Nutr
2006;83:282). This nutritional study was undertaken
as a component of the Nurses Health Study in the US
whereby 84,555 women were recruited between the
ages of 34 and 59 and followed for 20 years with
repeated assessments of diet. A number of clinical end-
points were determined, the onset of type 2 dia-
abetes being one of them. Previously considered to be
an integral part of a balanced, nutritious diet, the
humble potato – so long the mainstay of the Irish
diet – is a high glycaemic form of carbohydrate and
as such is thought to increase insulin resistance and
the risk of type 2 diabetes. There were 4496 new cases
of type 2 diabetes in the study group and detailed
risk assessment of dietary intake highlighted an asso-
ciation with potatoes and ‘French fries’ – or what we
call chips on this side of the Atlantic – among
them. However, the authors concede that diabetes
developed in the more obese individuals with seden-
tary lifestyles who are more at risk of the metabolic syn-
drome in any case, as well as the difficulty of teasing out
the exact contribution of potatoes among all the many
constituents of the unhealthy Western diet to the risk
calculations.

The Atkins diet, with its promotion of high-
protein, low-carbohydrate foods, has come in
for deserved scrutiny and criticism. A recent
case report documents a life-threatening complication
of this diet (Lancet 2006;367:958). An obese 40-year-old
Manhattanite in pursuit of the Carrie Bradshaw

Ann Clin Biochem 2006; 43: 522–524