15th European Congress of Endocrinology

Meet-the-Expert Handouts

A collection of handouts prepared by the Meet-the-Expert Speakers for the 15th European Congress of Endocrinology
ECE 2013 Meet-The-Expert Sessions

The speakers of the Meet-the-Expert sessions were given the opportunity to provide a handout to accompany their presentation to be available for all congress delegates. This represents a compilation of the texts provided by the speakers and has not been edited.

Please note that some of the speakers may not use a handout in conjunction with their presentation.

The Meet-the-Expert sessions are designed to be small interactive sessions that focus on extensive audience participation. They are informal conversational sessions with clinical practitioners noted for their teaching ability. Attendance at the sessions will be on a first-come, first-served basis. If the room is full, admittance will be denied.

Each of the 16 Meet-the-Expert sessions will be conducted twice throughout the congress. In the event that you are unable to attend either session, this booklet is designed to give an oversight of the topic discussed and the speakers’ approach to diagnosis and therapy.

The recommendations contained in this handout book may not apply to all patients as they are of a general nature. The opinions contained in this booklet represent those of the speakers and do not represent an official position of the European Society of Endocrinology.
<table>
<thead>
<tr>
<th>TOPIC / SPEAKER</th>
<th>DATE</th>
<th>TIME</th>
<th>ROOM</th>
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<tbody>
<tr>
<td><strong>MTE 1</strong></td>
<td>Sunday 28 April</td>
<td>11:25-12:10</td>
<td>Meeting Room 21</td>
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<tr>
<td>What systems biology can do for endocrine research</td>
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<td>M. Oresic</td>
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<td>Adult GH Deficiency replacement</td>
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<tr>
<td>Insulin treatment in T2 diabetes: When, Who and How</td>
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<td>I. Satman</td>
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<td>Viral vector-mediated gene transfer:</td>
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<td>A powerful tool for in vivo endocrine research</td>
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<td>F. Bosch</td>
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MTE 14
THIS SESSION HAS BEEN CANCELLED  Tuesday 30 April  12:15-  Main Hall  13:00

MTE 15
Molecular imaging in endocrinology  Tuesday 30 April  12:15-  Auditorium 10/11  13:00
A. Kjaer

MTE 16
Diabetic Foot Disease for Endocrinologists  Tuesday 30 April  12:15-  Auditorium 15  13:00
T. Coll
Insulin treatment in Type 2 Diabetes

Dr. Ilhan SATMAN
Istanbul University Faculty of Medicine
Division of Endocrinology & Metabolism

Disclosure
Advisory Panels
Bayer Diagnostic, MSD, Novartis, NovoNordisk, Pfizer, Sanofi

Current treatment goals*
- Glycated hemoglobin (A1C): <7%
- Fasting (FPG)/preprandial PG: 70 – 120 mg/dL
- Postprandial PG (PPG): <160 mg/dL

*Treatment goals must be individualized
Evolutionary development of drugs used in T2DM

**Slide 4**

Most patients on diabetes therapies do not reach A1C <7%

**Slide 5**

TURDEP-II: Glycemic control in known diabetes

**Slide 6**
Slide 7

Relative merits of hypoglycemic agents
Potency of hypoglycemic agents in monotherapy

![Graph showing the relative merits of hypoglycemic agents.](image)

Nathan et al, 2013

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Slide 8

Type 2 diabetes is a progressive disease and in UKPDS glycemic control deteriorates over time

![Graph showing the progression of glycemic control in UKPDS.](image)

Type 2 diabetes is a progressive disease and in UKPDS glycemic control deteriorates over time


* Diet initially then sulphonylureas, insulin and/or metformin if FPG>15 mmol/L

† ADA clinical practice recommendations. UKPDS 34, n=1704

Median A1C (%)

<table>
<thead>
<tr>
<th>Years from randomisation</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
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<tbody>
<tr>
<td>Conventional* (n=411)</td>
<td>7.5</td>
<td>8.5</td>
<td>6.5</td>
<td>5.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Glibenclamide (n=277)</td>
<td>7.0</td>
<td>8.0</td>
<td>6.0</td>
<td>5.0</td>
<td>4.0</td>
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<tr>
<td>Insulin (n=409)</td>
<td>7.0</td>
<td>8.0</td>
<td>6.0</td>
<td>5.0</td>
<td>4.0</td>
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<tr>
<td>Metformin (n=342)</td>
<td>7.0</td>
<td>8.0</td>
<td>6.0</td>
<td>5.0</td>
<td>4.0</td>
</tr>
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Slide 9

T2DM: Chronic condition with progressive beta cell loss.

![Graph showing the progression of beta cell function in T2DM.](image)


HOMA = homeostasis model assessment

β-cell function = 50% of normal

~50% of beta cell function already lost at diagnosis

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Slide 10

**Relative merits of hypoglycemic agents**

Second step combination with metformin

[Graph showing reduction in A1C (%)]

Nathan et al, 2013

Slide 11

**Obstacles of the insulin initiation**

- Delayed Dx of T2DM
- Delay in starting insulin failing OADs
- Fear of weight gain
- Fear of hypoglycemia
- Patient resistance to insulin
- Provider resistance to insulin
- Inappropriate care practices
- Insufficient support

Slide 12

**Indications for insulin therapy in patients with Type 2 diabetes**

- Symptomatic hyperglycemia (PG >250 mg/dL)
- Inadequate glycemic control (based on individual patient A1C >7% - A1C >8.5%)
- Intolerance or contraindications to OADs
- Long-term diabetes (not responding to OADs)
- Transient poor control (intercurrent illness, glucocorticoid therapy)
Goals of insulin therapy:
- Achieving patient-specific targets
  - A1C <7%
  - FPG & Pre-prandial PG: 70-130 mg/dL
  - 2-hPG <180 mg/dL
- Avoid frequent/severe hypoglycemias
- Minimize weight gain
- Reducing risk of microvascular disease

...without reducing Quality of Life!

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Slide 14

A1C low but not too low: Intensive glycemic control may increase risk of severe hypoglycemia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensive Control</th>
<th>Standard Control</th>
<th>% patients experiencing at least one severe hypoglycemic event</th>
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</thead>
<tbody>
<tr>
<td>VADT</td>
<td>2.7%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>16.2%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>21.2%</td>
<td>9.9%</td>
<td></td>
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</tbody>
</table>

A1C at study end: 7.3% vs. 6.4% vs. 6.9%

% change from baseline:
- VADT: 8.4% (P < 0.001)
- ACCORD: 1.0% (P < 0.001)
- ADVANCE: 7.5% (P < 0.001)

8.4% change in consciousness including loss of consciousness
16.2% requiring assistance of another person and plasma glucose < 2.8 mmol/l or symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or glucagon.
21.2% requiring assistance of another person and plasma glucose < 2.8 mmol/l.

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Slide 15

STEPS for drug selection:
- Safety
- Tolerability
- Effectiveness
- Price
- Simplicity
Slide 16

**Human Insulin Time-action Patterns**

- Normal insulin secretion at mealtime
- Regular insulin
- NPH insulin
- Premix 70/30

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Baseline level</th>
<th>Regular insulin</th>
<th>Premix 70/30</th>
<th>NPH insulin</th>
<th>Change in serum insulin</th>
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Slide 17

**Time-action Profiles of Human Insulins and Analogs**

- Aspart, Lispro, Glulisine (4–5 hr)
- Regular (6–8 hr)
- NPH (12–16 hr)
- Glargine/Detemir (~24 hr)


Slide 18

**Basal Insulins**

- Intermediate-acting
  - NPH
- Long-acting analogs
  - Glargine
  - Detemir
  - Degludec
### Slide 19: Pharmacokinetic profiles of insulins

<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Onset of action</th>
<th>Peak of action</th>
<th>Duration of action</th>
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<tbody>
<tr>
<td>Rapid-acting</td>
<td>&lt; ¼ - ½ h</td>
<td>½ - 1 h</td>
<td>1 - 3 h</td>
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<tr>
<td>Regular</td>
<td>½ - 1 h</td>
<td>2 - 3 h</td>
<td>3 - 6 h</td>
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<tr>
<td>NPH</td>
<td>1 – 3 h</td>
<td>6 – 8 h</td>
<td>12 – 16 h</td>
</tr>
<tr>
<td>Detemir</td>
<td>1 ½ h</td>
<td>Relatively peakless</td>
<td>12 – 24 h</td>
</tr>
<tr>
<td>Glargine</td>
<td>1 ½ h</td>
<td>Peakless</td>
<td>24 h</td>
</tr>
<tr>
<td>Degludec</td>
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### Slide 20: NPH insulin / Long-acting insulin analogs

<table>
<thead>
<tr>
<th>NPH</th>
<th>Glargine and Detemir</th>
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<tr>
<td></td>
<td>NPH insulin isophane suspension</td>
</tr>
<tr>
<td></td>
<td>similarities in absorption rates from different sites</td>
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<tr>
<td></td>
<td>Usually given once daily, once or twice daily</td>
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<td></td>
<td>Risk of hypoglycemia due to peak action</td>
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<td></td>
<td>Can be mixed with regular and rapid-acting analogs</td>
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### Slide 21: What is going on in the real World? Trends of insulin therapy 2002-2006*

Majority of patients are only taking a long-acting basal insulin.

*Data from 2006 U.S. Market.
Slide 22

FPG contributes to ≥50% of overall A1C when A1C over 8.4%

Adapted from Monnier L et al. Diabetes Care 2003;26:881-885.

Slide 23

**Bolus insulins**

- Short-acting
  - Regular
- Rapid-acting analogs
  - Aspart
  - Lispro
  - Glulisine

Slide 24

**Short-acting / Rapid-acting insulins**

<table>
<thead>
<tr>
<th>Regular insulins</th>
<th>Rapid-acting insulin analogs</th>
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<tr>
<td>Admin: 30-60 min before meal.</td>
<td>Admin: 10 min before meal.</td>
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<tr>
<td>Can be mixed with NPH</td>
<td>Can be mixed with NPH</td>
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<tr>
<td>This only insulin can be given i.v.</td>
<td>Replacement to regular insulin</td>
</tr>
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<td>Minimizes physiological prandial responses</td>
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Slide 25

Premixed human insulins

- Premixed human insulins:
  - 70/30 Mix HM: 70% NPH / 30% Regular
  - Dual peak
  - Must be injected 30 min before meals, twice daily
  - Advantages:
    - Convenience
  - Disadvantages:
    - Inability to adjust only one component
    - No nocturnal hypoglycemia
    - Patient must eat fixed time meals!

Slide 26

Premixed insulin analogs

- Premixed insulin analogs:
  - 70/30 AspartMix: 70% Aspart protamine / 30% Aspart
  - 75/25 LisproMix: 75% Lispro protamine / 25 % Lispro
  - One peak, followed by a ‘long tail’ (no NPH)
  - Must be injected 15 min before meals, once-thrice daily
  - Advantages:
    - Convenience
    - Flexibility with meals
    - Less nocturnal hypoglycemia
  - Disadvantages:
    - Inability to adjust only one component

Slide 27

Mimicking Physiology: Basal and Prandial Insulin

- Basal insulin:
  - Breakfast
  - Lunch
  - Dinner

- Prandial insulin:
  - Breakfast
  - Lunch
  - Dinner

- Basal insulin
  - Plus

- Prandial insulin
  - Daily

- Time:
  - 4:00
  - 8:00
  - 12:00
  - 16:00
  - 20:00
  - 24:00
Possible approach for adding insulin

- Starting basal insulin with continued OAD(s)
- Starting premixed insulin with metformin
- Discontinued OAD(s) initiating insulin regimens:
  - Premixed insulin
  - Prandial insulin with a basal once/twice daily.

Starting a basal insulin

Treat to Target study

- Continue oral agent(s) at same dosage
  - Do not stop insulin secreting agent.
- Add single, evening dose (0.1-0.2 IU/kg)
  - 10–20 IU
- Glargine, Detemir or NPH (bedtime)
  - Increase insulin dose every 3-4 days as needed
  - Increase 1-2 IU if FBG >150 mg/dL
  - Increase 1–2 IU if FBG: 130–150 mg/dL.
- Treat to Target FBG (<120 mg/dL)

Traditional sliding scale

- An arbitrary insulin dosing algorithm based on premeal glucose values only

<table>
<thead>
<tr>
<th>Premeal BG (mg/dL)</th>
<th>Insulin dose (IU)</th>
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<tr>
<td>&lt;151</td>
<td>0</td>
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<tr>
<td>151–200</td>
<td>2</td>
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<tr>
<td>201–250</td>
<td>4</td>
</tr>
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<td>251–300</td>
<td>6</td>
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<td>301–350</td>
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<td>351–400</td>
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<td>401–450</td>
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<td>451–500</td>
<td>15</td>
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<td>501–600</td>
<td>20</td>
</tr>
<tr>
<td>&gt;600</td>
<td>25</td>
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</table>
Adding a meal time bolus

Only FBG at target

1. Stop insulin secreting agents
2. Add bolus insulin before meals (regular or analog)
3. Isocaloric meals
   - Add 10 IU to regular insulin total dose to 40 IU
   - Patient taking 30 IU glargine needs 40 IU before meals
   - Calculate new total dose of 40 IU
   - 50% will be new basal (20 IU)
   - 50% is divided doses will be the meal time bolus (i.e., 10 IU)
4. Carb counting and correction factors
5. Blood glucose must checked! "Mind leading the blind"
6. Safety

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Slide 32

Total daily insulin

- Total daily insulin requirement is calculated based on body weight
  - T1DM: ~0.6 IU/kg (0.4 – 0.8)
  - T2DM: ~1.2 IU/kg (1.0 – 1.4)
- Blood glucose levels at goal without hypoglycemia
  - Basal: 40 – 50%
  - Bolus: 50 – 60% (meal doses)

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Slide 33

Calculating 'Basal & Bolus' insulins

- Calculate 'total daily dose' (TDD)
  - T1DM: ~0.6 IU/kg (0.4 – 0.8)
  - T2DM: ~1.2 IU/kg (1.0 – 1.4)
  - Basal: 40 – 50% of TDD
  - Bolus: 50 – 60% of TDD
- Divide equally for three meals or
- Insulin sensitivity factor (ISF): 1700/TDD
- Carbohydrate/Insulin ratio (CH/I): 500/TDD
  - Patient BS – Target BS + Correction factor
  - Now add carb ratio for meal
### Slide 34
**Case example 1**
- **RSÇ, 57 yrs Men, 9 yrs w T2DM**
- **Wt**: 95 kg, **Ht**: 1.76 m, **BMI**: 30.7 kg/m²
  - **TDD**: 95 x 1.2 = 114 IU
  - **Basal dose (50% of TDD)**: 57 IU
  - **Bolus dose (50% of TDD)**: 57 IU
  - **Isocaloric meals**
    - Each bolus: 57/3 = 19 IU
    - **CH/I**: 500/114 = 4.4
    - 1 IU insulin for every 4.4 g CH
  - **ISF**: 1700/95 = 18
    - 1 IU insulin lowers BG 18 mg/dL

### Slide 35
**Above target at breakfast**
- **Pre-meal target**: 120 mg/dL
- **FPG**: 220 mg/dL
- **Dinner**: 60 g CH
  - 220 - 120 = 100 mg/dL, too high before eating
- **ISF**: 18
  - 100/18 = 5.6 IU (will need to correct to target)
  - **CH/I**: 4.4
    - 60/4.4 = 13.6 IU (will need for breakfast)
  - 5.6 IU + 11.6 IU = ~17 IU before breakfast

### Slide 36
**Below target at dinner**
- **Pre-meal target**: 120 mg/dL
- **Pre-dinner BG**: 80 mg/dL
- He'll be eating 75 g CH
  - 80 - 120 = 40 mg/dL, too low before dinner
- **ISF**: 18
  - 40/18 = 2.2 IU (will need 2.2 IU less to correct to target)
  - **CH/I**: 4.4
    - 75/4.4 = 17.1 IU (will need for the dinner)
  - 17 - 2.2 = ~15 IU before dinner
Slide 37

What should be the dose range in T2DM?

- Range: 0.3 – 1.2 IU/kg
- Thin – more insulin deficient
  - U-100 insulins
- Obese/overwt – more insulin resistant
  - U-100 insulins
- Most needs 1.0 – 1.2 IU/kg
  - Basal: 50 – 60%
  - Prandial: 50 – 50%

Slide 38

Non-syndromic insulin resistance
U-500 insulins may be beneficial?

- When 100 IU (1 mL) insulin required at one time, may need more than one injection
- Large volume of insulin may be painful
- Large depot of insulin impedes absorption making it unpredictable
- Some patients may require >200 IU/day
  - Obesity with T2DM post-op or post-Tx states
  - High dose steroids or pressors
  - Pregnancy with underlying T2DM
- In this case U-100 insulin may be impractical and inconvenient
- U-500 insulin?

Slide 39

Injection problems

- Lipodystrophy
  - Immunologic mechanism
  - Breakdown (pitting) of fat tissue
  - Indentation in the skin
- Lipohyperthrophy
  - Thickening (lumps) of SQ fat
  - Repeated injections in the same site, re-used needles
  - Delays insulin absorption
- Bruising at site
  - Improper technique
Insulin delivery systems

• Syringes
  - 12.7 mm, 8 mm
  - 28–32 G
  - 1 mL, ½ mL, ¼ mL, 3/10 mL

• Insulin pens
  - 28–32 G
  - 8 mm, 12.7 mm, 5 mm, 4 mm

• Continuous insulin infusion pump
  - Use bolus insulin only

Expiry dates of the available insulins administered via pen

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Once opened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular insulins</td>
<td>28 days</td>
</tr>
<tr>
<td>Rapid-acting analogs</td>
<td>28 days</td>
</tr>
<tr>
<td>Basal insulins</td>
<td>14 days</td>
</tr>
<tr>
<td>NPH insulins</td>
<td>14 days</td>
</tr>
<tr>
<td>Glargine insulin</td>
<td>28 days</td>
</tr>
<tr>
<td>Detemir insulin</td>
<td>42 days</td>
</tr>
<tr>
<td>Premixed insulins</td>
<td></td>
</tr>
<tr>
<td>70/30 Human insulins</td>
<td>10 days</td>
</tr>
<tr>
<td>75/25 Lispro insulin</td>
<td>10 days</td>
</tr>
<tr>
<td>70/30 Aspart insulin</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Intensive therapy of T2DM

Minimise hypoglycaemia
No weight gain
No excess CVD
Effort
Expense

Reduced development or progression of Microvascular complications
**Slide 43**

Clinical Inertia: Specialists do not give better care than Primary Care

![Graph showing clinical inertia comparison between specialists and primary care.]


**Slide 44**

Less than 100 years...

![Comparison of medical devices: Mr. Sensor and Ms. Pump.]

1922 vs. 2010

**Slide 45**

Insulin Pump treatment: Initial adjustment

- Proposed Total Daily Insulin (TDI)
- Reduce by 20-30%

- Daily pump dose
  - Basal
  - Bolus (before meals)
  - Adjustment

Conclusions

1. T2DM needs to be viewed as a progressive disease.
2. At present, insulin is one of the therapies available to treat diabetes, not as a treatment of last resort and not as a punishment.
3. There is a short- and long-term advantage of good glycemic control.
4. Reframe the message as “transition to insulin” rather than “failure of OADs.”
5. Reflect on perception of insulin therapy and avoid using negative terms (e.g., “We need to put you on injection.”)
7. Give more time to each modern aspects of basal-bolus insulin therapy (e.g., correction factors).

Thank you
Isabelle Runkle de la Vega
Department of Endocrinology, Metabolismo and Nutrition
Hospital Clinico San Carlos
Madrid

Management of Hyponatremia

To correctly manage hyponatremia:

- It must be NOTICED
- Its symptoms recognized
- Correctly classified
- Correctly diagnosed

**Hypovolemic hyponatremia**

| Total body water is diminished! |

**Hypervolemic hyponatremia**

| Increased body water, in wrong place |

**Low Effective Circulating Volume**

- Decreased renal perfusion
- ADH stimulated via baroreceptors

**The nephron reabsorbs more water**
### Low effective Circulating Volume

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>PHYSICAL EXAM</th>
<th>LAB TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Causes</td>
<td>OP</td>
</tr>
<tr>
<td>Translocaional hyponatremia</td>
<td>Diabetes, Mannitol</td>
<td>N or LOW</td>
</tr>
<tr>
<td>Pseudohypo natremia</td>
<td>Hyper lipidemia</td>
<td>N</td>
</tr>
</tbody>
</table>

### “Euvolemic”: Normal or elevated Effective Circulating Volume

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>PHYSICAL EXAM</th>
<th>LAB TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Causes</td>
<td>OP</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>Without heart failure</td>
<td>N</td>
</tr>
<tr>
<td>Primary polydipsia</td>
<td>Worse if low Na intake, stre</td>
<td>N</td>
</tr>
<tr>
<td>Acute water intoxication</td>
<td>Can stim AVP via nausea</td>
<td>N</td>
</tr>
<tr>
<td>Low Na intake</td>
<td>With adequate fluid intake</td>
<td>N</td>
</tr>
<tr>
<td>ADH Family</td>
<td>SIADH, SIAD, 2ary adrenal insufficiency, Severe hypothyroidism, Post-op, nausea, Pain, Thiazides</td>
<td>N</td>
</tr>
</tbody>
</table>

Case studies will be presented
Current guidelines for the classification of GEP NENs

Guido Rindi
Istituto di Anatomia Patologica
UCSC, Policlinico A. Gemelli,
Roma

NEUROENDOCRINE NEOPLASMS

NERVE STRUCTURES
Ganglioneuroma*/**
Neuroblastoma*/**
Paraganglioma*/**

DIFFUSE NEUROENDOCRINE SYSTEM
GEP NE neoplasms*
lung carcinoid, LCNEC, SCLC*
skin Merkel cell ca
other anatomical sites**

ENDOCRINE GLANDS
pituitary adenoma/ca*
parathyroid adenoma/ca*
thyroid medullary ca*
pheochromocytoma*

* Digestive system (WHO 2010)
Lung, Pleura, Thymus and Heart (WHO 2004)
Endocrine organs (WHO 2004)

**Head and Neck (WHO 2005)
Breast (WHO 2003)
Urinary system (WHO 2004)
# Gastroenteropancreatic Neuroendocrine Neoplasms

## Heterogeneity, Anatomical Site and Clinical Behavior

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Main Cell Type</th>
<th>Stomach</th>
<th>Intestine</th>
<th>Possible Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Carcinoid&quot;</td>
<td>B +</td>
<td>Pa CF An</td>
<td>D J I Ap C R</td>
<td>insulinoma</td>
</tr>
<tr>
<td></td>
<td>A +</td>
<td></td>
<td></td>
<td>glucagonoma</td>
</tr>
<tr>
<td></td>
<td>PP +</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(PP?) +</td>
<td></td>
<td></td>
<td>WDHA; ACTH; calcitonin somatostatinoma</td>
</tr>
<tr>
<td></td>
<td>D + + + + + +</td>
<td></td>
<td></td>
<td>&quot;carcinoid&quot;</td>
</tr>
<tr>
<td></td>
<td>EC + + + + + +</td>
<td></td>
<td></td>
<td>&quot;atypical carcinoid&quot;</td>
</tr>
<tr>
<td></td>
<td>ECL +</td>
<td></td>
<td></td>
<td>ZES</td>
</tr>
<tr>
<td></td>
<td>G + + + +</td>
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<td></td>
<td>L + + + + + +</td>
<td></td>
<td></td>
<td>(?)</td>
</tr>
<tr>
<td></td>
<td>Ghrelin + +</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"Small Cell Carcinoma"

<table>
<thead>
<tr>
<th></th>
<th>S/I</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Small Cell Carcinoma&quot;</td>
<td>+ + + + + + + + + + + + +</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Site-Dependent Cell Heterogeneity and Clinical Behavior**

*Modified From Digestion 2000, 62(3):19*

## Gastroenteropancreatic Neuroendocrine Neoplasms

## Heterogeneity, Anatomical Site and Clinical Behavior

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<tr>
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<td></td>
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<td></td>
<td>(PP?) +</td>
<td></td>
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<td>WDHA; ACTH; calcitonin somatostatinoma</td>
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<td></td>
<td>EC + + + + + +</td>
<td></td>
<td></td>
<td>&quot;atypical carcinoid&quot;</td>
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<td>G + + + +</td>
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<td>L + + + + + +</td>
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<td></td>
<td>(?)</td>
</tr>
<tr>
<td></td>
<td>Ghrelin + +</td>
<td></td>
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"Small Cell Carcinoma"

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<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>+ + + + + + + + + + + + +</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**No Site-Dependent Cell Heterogeneity and Clinical Behavior**

*Modified From Digestion 2000, 62(3):19*
**NEUROENDOCRINE NEOPLASMS**

**The Significance of Grading**

<table>
<thead>
<tr>
<th>Neuroendocrine Tumor</th>
<th>Definition</th>
<th>Behavior</th>
<th>Functional activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET G1</td>
<td>benign-low grade malignant*</td>
<td>variable</td>
<td></td>
</tr>
<tr>
<td>NET G2</td>
<td>benign-low grade malignant*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Neuroendocrine Carcinoma**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Behavior</th>
<th>Functional activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC**</td>
<td>high grade malignant</td>
<td>absent/variable</td>
</tr>
</tbody>
</table>

*depending on stage

**WHO 2010**

**Working Principles**

**Grading**

**GEP Neuroendocrine Neoplasms**

**Tumor Grading and Classification**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Grade</th>
<th>Mitotic count (per 2.0 HPF)</th>
<th>Ki67 index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET G1</td>
<td>2</td>
<td>≤2</td>
<td>≤2</td>
</tr>
<tr>
<td>NET G2</td>
<td>2-20</td>
<td>2-20</td>
<td>2-20</td>
</tr>
<tr>
<td>NEC G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

*For methods: HPF (high-power field), NET = neuroendocrine tumor, NEC = neuroendocrine carcinoma, Ki67 = nuclear labeling index.*

**General Neuroendocrine Neoplasms Categories WHO 2010**

1. Neuroendocrine tumor, NET G1
2. Neuroendocrine tumor, NET G2
3. Neuroendocrine carcinoma, NEC (small or large cell type)
4. Mixed adenoneuroendocrine carcinoma, MANEC
5. Hyperplastic and preneoplastic lesions

**GEP Neuroendocrine Neoplasms WHO General Categories**

1. NET G1
2. NET G2
3. NEC (small cell & large cell carcinoma)
4. Mixed adenoneuroendocrine carcinoma
5. Hyperplastic & preneoplastic lesions

**Marker Expression in Neuroendocrine Neoplasms**

- LDCV antigens
- SSV antigens
- Cytosol antigens
- KI67 index
- PS3
- Hormones
- Membrane antigens
- FAL/AII/CIN

*Source: F.T. Camerino, F. Huber RH, The WHO Classification of Tumours of the Digestive System, 2010*
NEUROENDOCRINE NEOPLASMS
Grading limits and open questions

1. Is G1-G2 Ki67 2% cut-off still effective at all sites?
   - All evidence supports the prognostic significance of Ki67 grading as general rule, but site-specific adjustments may be adopted (see pancreas)

2. The G2 group is large (Ki67 3-20%); different cancer types?
   - Specific Ki67 definition appears mandatory for therapy tailoring – generate data

WHO 2010 working principles

- TNM recommended (AJCC-UICC-WHO 2010)
  - for “carcinoids” only (excludes G3 neoplasms)
  - blueprint from ENETS proposals 2006-2007 for stomach, ileum & colon, but with significant differences for appendix and pancreas (generate data)

- New data for pancreas support the ENETS scheme

- Diagnosis by site according to the above uniform grading and staging parameters

- Minimal histopathology report recommendation
  - Neoplasm definition as NET or NEC
  - Grade definition as G1-G3
  - pTNM definition (when possible)

NEUROENDOCRINE NEOPLASMS TUMOR GRADING AND CLASSIFICATION

SUMMARY

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Tumor definition</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well moderately differentiated</td>
<td>NET</td>
<td>WHO 1, G1</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>NEC</td>
<td>WHO 2, G2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WHO 3, G3</td>
</tr>
</tbody>
</table>

NEUROENDOCRINE NEOPLASMS

GEP NEUROENDOCRINE NEOPLASMS

Therapeutic Algorithm

- Surgery (resection, debulking, RF embolization)
- Biotherapy
  - Somatostatin analogue (SMS)
  - α-IFN
  - Combination on
  - SMS + α-IFN
  - SMS + Everolimus
  - SMS + bevacizumab
- Chemotherapy
  - ST75/FU/Box
  - STZ + RAD001
  - Temozolomide + capcitabine
  - SMS for symptom control
- Targeted Radiotherapy
  - Lu177 DOTA-octreotate, Y90 DOTATOC
- Experimental Protocols

*SMS also in WHO 2 and 3 for symptomatic control

Oberg et al. Am Oncol 2010, 21(55):229
**GEP NEUROENDOCRINE NEOPLASMS**

Current guidelines for the classification of GEP NENs

**conclusions**

- Neuroendocrine neoplasms have different phenotype and molecular background
- Neoplasm classification reflects tumor biology knowledge into different entities at different sites
- WHO 2010 stems for WHO 2000 and introduces grading and TNM staging
- Therapy strictly depends on neoplasm type (site!), grade and stage
- Specific targets and relevant targeted molecules do exist: more hopefully to come!

**THANKS**

The ENETS Guidelines Consensus Meetings 1 & 2 Team

Frascati, November 2-5, 2006 / November 1-4, 2006

The WHO 2010 Eds F.T. Bosman, F. Carneiro, R.H. Hruban and N.D. Theise, the digestive pathology team, the endocrine crew and all WHO staff

Lyon, December 8-12, 2009
Rationale for the use of Rituximab (RTX) in Graves’ disease (GD) and orbitopathy (GO).

The availability of the B cell depleting agent RTX has provided the rationale of its use in GD, since it was thought that blockade of pathogenic autoantibody generation might bring about GD remission. Furthermore, since Graves’ hyperthyroidism is autoantibody mediated, such therapy would have been effective by specifically targeting TSAb, the stimulating subpopulation of Igs among TRAb. Other additional functions of B cells in thyroid autoimmunity are potential targets for RTX therapy, e.g. their role as antigen-presenting cells and their capability of producing cytokines, mostly pro-inflammatory, as described previously.

Biologic markers of B cell depleting therapy with RTX.

In order to effectively use biologic therapies in autoimmune diseases it is necessary to target patients with the highest likelihood of response. Until now, in thyroid autoimmune disorders the limited evidence available derives mainly from open studies or even single patients reports treated with RTX. In such a context, the analysis of the few data available has to rely necessarily on the observation of a number of biologic markers that have been suggested as suitable and necessary for evaluating the efficacy of RTX. These include traditional markers, such as circulating levels of Ig and specific autoantibodies, e.g TRAb, TSAb, anti-thyroglobulin and thyroperoxidase antibodies, as well as markers specifically related to the mechanisms of action of the B cell depleting compound, such as peripheral or intra-tissue B cells, and the levels of cytokines. In addition, other important markers such as circulating IL-10 or BAFF/APRIL should be measured in relation to the effectiveness of therapy and the possible side effects. Efficacy of RTX treatment needs also validation of the impact on the clinical course of the disease by the measurement of changes in clinical parameters, such as remission or relapse of hyperthyroidism in GD and improvement of the orbital inflammatory signs in GO, as assessed by the disease’s clinical activity score (CAS) [79] and the NOSPECS score for severity [80].
Effects of RTX on GO.

To date, the effects of RTX in patients with active GO have been studied in no more than 50-60 patients. Although caution is suggested before proposing RTX as a novel therapeutic tool in this disease, nonetheless the data collected show that RTX does significantly affect the inflammatory activity and severity of GO. The first evidence of efficacy of RTX in active GO was reported in one patient unresponsive to standard i.v. methylprednisolone therapy [Salvi et al. 2006]. She was euthyroid on MMI and had well controlled type 1 diabetes. The clinical response was characterized by consistent decrease of the CAS (<3) and improvement of ocular motility, but not of hyperthyroidism. In fact she had relapse of hyperthyroidism with a surge of serum TRAb, while being B cell depleted and eventually underwent thyroidectomy. RTX induced peripheral B cell depletion for up to six month after two i.v. doses of 1000 mg and intra-orbital B and T cell depletion at 10 months (see below). El Fassi et al. [2006] treated two women with active GO, also resistant to glucocorticoid therapy, with 4 weekly doses of RTX of 375 mg/m². At eight months after treatment, the CAS had decreased from 5 and 6 to 1 and 2, respectively and soft tissue changes, eye motility and proptosis significantly improved in both patients. In both reports the anti-inflammatory effect of RTX was observed as early as 4-6 weeks after therapy and persisted without disease relapse and any additional therapy. In an open study of Salvi et al. [2007] nine patients with active GO, of whom two had only lid signs, were treated with RTX and compared with a group of 20 patients treated with the standard i.v. methylprednisolone therapy. All patients responded to RTX therapy compared to 80% of those treated with steroids. CAS values significantly decreased from 4.7 to 1.8 at the end of follow-up and more rapidly compared with steroids. Proptosis, eye muscle motility and signs of soft tissue inflammation also improved significantly in response to RTX. Relapse of active GO was not observed in patients treated with RTX, but occurred in 10% of those treated with steroids, who also experienced adverse effects more frequently (45% vs 33% of patients) (Table 4). More recent data have confirmed that RTX favourably affects active GO. Khanna et al. [2010] have reported that in six patients with active and severe GO, unresponsive to glucocorticoid therapy, RTX had a rapid and sustained therapeutic effect on both
activity and severity. In this study RTX was infused i.v. as 1g twice with two a week interval concomitantly with steroid therapy. The CAS decreased from 5.5 to 1.8 at eight weeks after RTX and remained persistently low at six months. No patients showed improvement of extra-ocular motility or proptosis, but in four of these patients who had optic neuropathy, visual acuity improved within 4 weeks and returned to pre-morbid values at eight weeks from treatment. Tapering of glucocorticoids was not followed by relapse of inflammatory signs. A significant therapeutic effect of RTX was also recently reported by other groups [Silkiss, 2010, Mitchell, 2013] in patients with active GO who eventually showed complete and persistent inactivation of GO. In contrast to all these reports, failure of RTX in improving GO and subsequent progression to optic neuropathy in a single patient was reported [Krassas 2010]. The number of GO patients treated with RTX is, until now, limited to small series or single patients with different thyroid status, severity of GO and previous, often unsatisfactory treatment. A novel treatment for GO is most needed, and only controlled studies will at this point provide evidence on the efficacy and safety of RTX. These studies will also help us in deciding whether RTX is to be used as a first line therapy in any patients with active GO or only in those with otherwise unresponsive disease of severe degree.

Mario Salvi, M.D.
Secretary, European Group on Graves’ Orbitopathy,
Graves’ Orbitopathy Center,
Endocrinology Unit,
Fondazione Ca’ Granda IRCCS,
University of Milan,
Via Sforza 35, 20122 Milan, Italy
mario@mariosalvinet.it
DVDs with a video that has been prepared in the EU project "Clinigene" to introduce the gene therapy field to a general audience will be distributed at this session.

This video can also be found in the following link:

Cushing’s syndrome is considered as a rare disease. Although Cushing’s syndrome is clinically easily recognizable when full blown, one obstacle for its diagnosis is its broad spectrum of presentation. Specific symptoms reflecting protein-wasting may be subtle or lack in a number of patients. Since the degree to which signs and symptoms are detectable is dependent not only on their severity but also on the skills of the physician, one may hypothesize that the spectrum of clinical presentation may lead to underdiagnosis and that the “true” prevalence of Cushing’s syndrome may be higher than that quoted in population-based studies. This hypothesis is suggested by several screening studies performed in patients harboring clinical symptoms belonging to Cushing’s syndrome but in whom no specific clinical sign was found. The pathological situations in which screening for Cushing’s syndrome has been performed includes type 2 diabetes, obesity, osteoporosis and hypertension. Unrecognized Cushing’s syndrome in these situations may be referred as Occult Cushing’s syndrome. A screening strategy has to be faced with the elevated prevalence of diseases such as type 2 diabetes, obesity and hypertension in many countries. Thus a crucial point is to estimate the pertinence of a widespread screening of patients with a common disease for a rare one. Indeed, screening is only justified when there is enough evidence of its efficacy and that its benefits will outweigh its drawbacks. The potential indication of screening is based on a set of different criteria: the burden of the targeted condition, as evaluated by its frequency and severity; the natural history of the disease that should ideally include a latent or preclinical stage to allow early diagnosis and intervention; the diagnostic accuracy of tests must be high and the assessment of diagnostic accuracy needs the existence of a reference standard; the detection of the disease is only useful if treatment improves clinical outcomes. Screening expose individuals to investigations that are of no use to most of them and patients with false positive results will get only
the adverse effects of screening without the benefits. Finally, a screening program must be acceptable by professionals and the health-care system, in terms of work load and costs.

*Subclinical Cushing’s syndrome*, a semantic ambiguity, is closely related to Occult Cushing’s syndrome since it refers to relatively mild and autonomous cortisol production that is insufficient to generate a typical, clinically recognizable syndrome. The first description of Subclinical Cushing’s syndrome was performed in 1974 in front of two patients with no clinical evidence of Cushing’s that harbour a unilateral adrenal adenoma and exclusive uptake of noriiodocholesterol. In vivo demonstration of excessive cortisol production by the tumour responsible for this scintigraphic pattern came from catheterization studies that showed a larger cortisol output in the adrenal vein from the tumour side with contralateral suppression and scintigraphic reappearance of the contralateral gland after ACTH infusion or several months after removal of the tumour. Since then, so-called subclinical Cushing’s syndrome has been described in 5–30% of patients with adrenal masses found incidentally during the evaluation of unrelated diseases using abdominal imaging. The issue of subclinical Cushing’s syndrome in patients with adrenal incidentalomas is currently a common and very controversial issue in endocrine practice. Firstly there is no consensus on the biological criteria to diagnose subclinical Cushing’s syndrome and various diagnostic criteria have been used across studies. The diagnosis of subclinical Cushing’s syndrome is difficult for many reasons. One important concept is that there is no clear dichotomy between normal and abnormal cortisol secretion and that there is a spectrum of biological activity between tumors that ranges from the non functioning adenoma to the evident cortisol secreting tumor. Attempts to correlate the results of biochemical tests with clinical expression or clinical outcomes after surgical excision of the adrenal incidentaloma have yield to debatable results. Therefore, the diagnosis of subclinical Cushing’s syndrome relies more or less on arbitrary thresholds of cortisol levels during common biological evaluations of the HPA axis. Another point of difficulty is spontaneous fluctuation in cortisol secretion, a common finding in overt Cushing’s syndrome that may amplify the risk of misdiagnosis in mild hypercortisolism where biological endocrine abnormalities fluctuate around the limits of normal. Aside from diagnostic issues, whether subclinical Cushing’s syndrome associated with adrenal incidentalomas is an adverse condition is another point of debate. Several studies suggest that patients have an increased risk of metabolic and cardiovascular diseases but most studies suffer from referral bias. To date we lack prospective, long-term observational studies that provide evidence-based knowledge of extent to which subclinical Cushing’s syndrome is an adverse condition. The ultimate justification for diagnosing subclinical Cushing’s syndrome would be the demonstration that removal of the adrenal incidentaloma reverses end-organ complications. Although most reports acknowledge an improvement in blood pressure levels after surgical excision,
intervention studies suffer from major methodological bias such as: small number of patients studied, variable biological criterion for the diagnosis of subclinical Cushing’s syndrome, retrospective design, lack of knowledge on the selection of those who were operated, lack of comparison group treated with actual available pharmacological tools for diabetes or hypertension. Therefore to date no definitive conclusion can be drawn on the benefit of cure of subclinical Cushing’s syndrome. The duration and modalities of follow-up of patients that are not operated on is another point of debate.

A peculiar situation of subclinical Cushing’s syndrome is the early stage of recurrence of patients operated for Cushing’s disease. Approximately 15 to 25% of the patients who achieve early surgical remission will recur during long-term follow-up. It is thus recommended to perform a prolonged follow-up to ensure remission after surgery and detect as soon as possible recurrences in order to avoid prolonged exposure to an atherogenic milieu. However, the natural history of recurrence following surgery is poorly documented. Common experience and few studies suggest that it is often a progressive process during which mild hypercortisolism precedes the recurrence of clinical symptoms and overt hypercortisolism. Classical markers of hypercortisolism such as increased urinary free cortisol may be relatively delayed compared to other tests such as abnormal dynamic testing such as an aberrant response to the desmopressin test or an altered circadian rhythm of cortisol secretion.
LEARNING OBJECTIVES

- Recognize the scope of the subclinical Cushing’s syndrome problem
- Discuss the biological definition of subclinical Cushing’s syndrome and know the usual pitfalls in the biological evaluation of the HPA axis in patients with adrenal incidentalomas
- Discuss the opportunity to remove surgically adrenal incidentalomas associated with subclinical Cushing’s syndrome
- Identify patients in whom screening for occult Cushing’s syndrome should be considered
- Discuss the strategy to identify recurrence of Cushing’s disease in operated patients at an early stage

PERTINENT REFERENCES

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I have nothing to disclose

CASE 1

A 14-yr-old boy was referred to pediatric endocrinologist due to delayed puberty. His elder brother had died of bilateral renal agenesis at the age of few hours; otherwise his family history was unremarkable. He had a history of cryptorchidism, and now presented with small testes (<1 ml l.a.), no pubic hair, and inability to smell. In addition, he displayed mirror movements in hands. His testosterone (<0.2 nM), inhibin B (11 ng/l), AMH (2.5 ng/ml) and gonadotropin levels were all low. He had no signs or evidence of chronic diseases that could have accounted for his pubertal delay.

DISCUSSION POINT #1: We will discuss the diagnostic and differential diagnostic work-up of this boy. The etiology, frequency, and molecular genetic aspects of his condition will be discussed.
CASE 2

This man was initially referred to endocrinologist at the age of 28 years. He had decreased sense of smell, history of partial puberty, high-pitched voice, and no facial hair. He was diagnosed with Kallmann Syndrome and started on testosterone replacement therapy (TRT). Seven years later, testosterone was replaced by combined gonadotropin treatments to induce spermatogenesis. After only a few months, his wife became pregnant and gave birth to a baby girl that was soon diagnosed with unilateral microptalmia and bilateral coloboma.

DISCUSSION POINT #1: Should we suspect a link between the father’s and daughter’s phenotypes?

...CASE 2 continued...

After the successful induction of spermatogenesis, he was switched back to TRT. Unexpectedly, he fathered his second child while on TRT and did not therefore require gonadotropin therapy to induce spermatogenesis this time.

DISCUSSION POINT #2: Why he did not need gonadotropin or GnRH therapy to induce spermatogenesis?
CASE 3

This girl was referred to pediatric endocrinologist at the age of 16 years due to absent puberty. She had anosmia, and severe gonadotropin deficiency, findings consistent with Kallmann Syndrome (KS). His father also had KS, but had fathered 4 children without infertility treatments. Her brother had normosmic hypogonadotrophic hypogonadism. At the age of 28 yrs, following infertility treatments, she gave birth to a baby boy.

**DISCUSSION POINT #1**: We will discuss the diagnostics of congenital hypogonadotrophic hypogonadism in infants.
"I’m a physician- get me out of here!" Endocrinologists are trained to assess pathophysiology in an integrated and holistic manner, are well used to working in multidisciplinary teams in other aspects of their practice and are therefore well placed to take on an important role at the heart of a service addressing the needs of a fragile patient group. The heterogeneity of the patient population makes definitive guidelines a challenge and the lack of a robust evidence base for many interventions can engender a lukewarm response in the face of a pressing clinical need. However, there is much that can be done and tackling each component of the problem in a reasoned manner can pay huge dividends for the patient.

Make a fuss about feet wherever you go.

The humble foot is neglected, derided and mocked. It needs allies. Make a fuss on every ward round and clinic and protect fragility whenever you encounter it. Continue to avoid the avoidable.

Neuropathy- the silent enemy.

Lack of pain in a swollen, red foot should always ring alarm bells. Sensory neuropathy means even slight antecedent trauma is not recalled and damaging foreign bodies go unnoticed. Continued weight bearing in these circumstances can jeopardise the stability of the foot. In the patient has sensory neuropathy, when a foot “flare ups” with no apparent cause, further imaging is mandatory.

Shoes. Shoes should be foot shaped. Match the site of the lesion to its corresponding spot in the shoe-are there clues in the shoe to indicate that part of the foot is under pressure? Until pressure is taken off, the lesion will
not heal. This can often be done by simply changing footwear to a shoe that will accommodate the foot shape but often requires more specialist attention (total contact insole, bespoke footwear).

**Diabetic, not stigmatic.**

If a lesion is found, ask yourself- “Why this lesion in that position on that foot?” Lesions do not appear by magic and a simple history, seeing how the patient weight bears on their foot when standing plus a review of the footwear they were (or were not!) wearing when the lesion developed can be hugely informative.

**The frequent attender.**

Develop a healthy degree of neurosis around patients who previously have had an amputation and then go on to develop a new lesion. Previous damage predicts future loss. The same pathological processes which led to loss before are likely still to be at play and further problems (particularly worsening vascular insufficiency) may have accrued over time. It is one thing to live life with a single below knee amputation but quite another to be a bilateral amputee.

**Make friends with your surgeons.**

If the only time you speak to your surgeons is when you need something amputating, you’re doing it wrong. Vascular surgeons are typically closely aligned with interventional radiologists, have access to state of the art imaging equipment and would much rather work to restore circulation to an ischaemic limb than remove it. Orthopaedic surgeons can realign and reshape damaged bones into functional, weight bearing units and transform a person’s mobility and life.
**Be aggressive and tackle the acute foot with vigour.** No dressing in the world will ever compensate for inadequate footwear, vascular insufficiency or untreated infection. Consider an evolving foot lesion an acute medical emergency and treat it with the urgency it deserves.

![Foot diagram]

**A multisystem disorder.** Patients with diabetes related foot disease are typically burdened with a large number of chronic co-morbidities. Immobility, sepsis and ischaemia can significantly impact upon whole body metabolism. Equally, without care and attention to cardiac, renal, respiratory and metabolic abnormalities, meaningful healing is a major challenge.

Tony Coll, Cambridge, March 2013