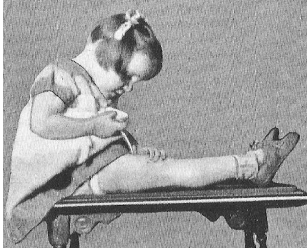
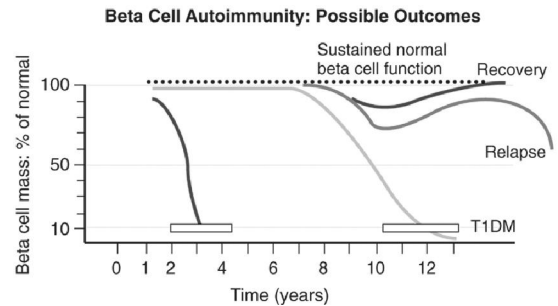


Insulin Therapy

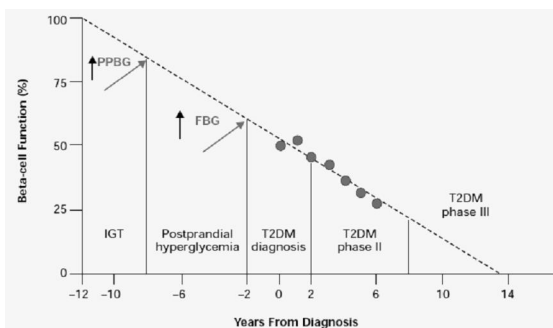
DG van Zyl



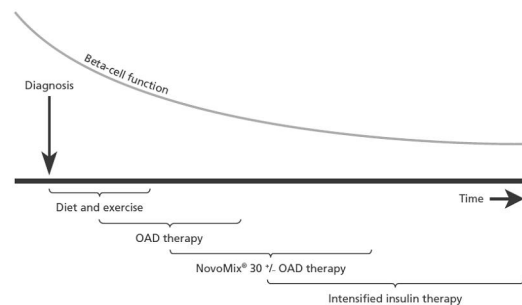
Type 1 Diabetes



Type 2 Diabetes



Type 2 Diabetes



Glycaemic Targets

| | Good | Borderline | Poor |
|---|-------|------------|-------|
| Fasting glucose (Mmol/l) | 4 – 7 | 7-8 | > 8 |
| Glucose 2 hours postprandially (Mmol/l) | < 9 | 9-10 | > 10 |
| HbA _{1c} (%) | < 7 | 7 – 8.5* | > 8.5 |

Major advances in insulin development

| | | |
|------|------------------------------|--|
| 1922 | Isolation of insulin | Banting & Best |
| 1934 | Zinc-insulin crystallization | Scott <i>et al.</i> |
| 1936 | Protamine insulin | Hagedorn <i>et al.</i> Scott & Fisher |
| 1946 | Isophane insulin, NPH | Krayenbühl & Rosenberg |
| 1952 | Lente series | Hallas-Møller <i>et al.</i> |
| 1961 | Neutral regular insulin | Schlichtkrull <i>et al.</i> |
| 1972 | Monocomponent insulin | Schlichtkrull <i>et al.</i> |

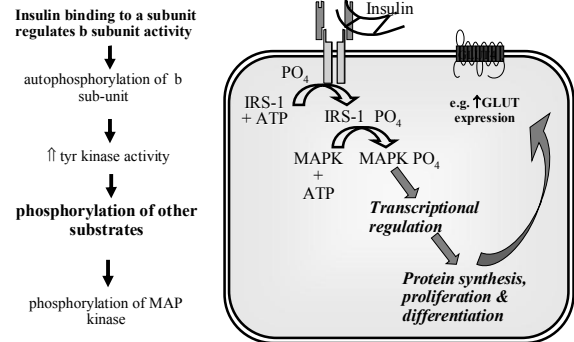
Adapted from Brange, *Diabetes Care* 1990;13:923-954.

Development of semi- and biosynthetic insulin

| | | |
|------|---------------------------------|-------------------------------|
| 1977 | Cloning of the rat insulin gene | Ullrich <i>et al.</i> |
| 1979 | Porcine to human insulin | Markussen <i>et al.</i> |
| 1979 | Human insulin in <i>E. coli</i> | Goeddel <i>et al.</i> |
| 1986 | Human insulin in yeast | Markussen, Thim <i>et al.</i> |
| 1987 | Rapid-acting insulin analogues | Brange <i>et al.</i> |
| 1987 | Long-acting insulin analogues | Markussen <i>et al.</i> |

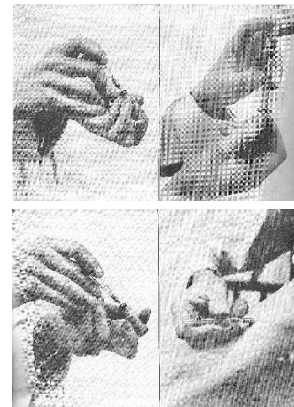
Adapted from Brange, *Diabetes Care* 1990;13:923-954.

Insulin Receptor Signaling

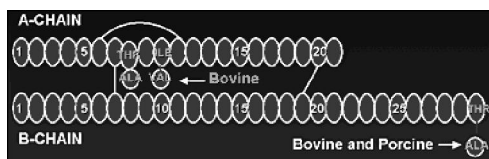


Insulin action

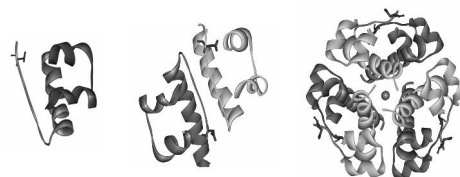
1. Increases glucose uptake, particularly in muscle, liver and adipose tissue
2. Suppresses glucose output from the liver
3. Increases formation of fat
4. Inhibits breakdown of fats
5. Promotes amino-acid uptake and prevents protein breakdown



Insulin Structure

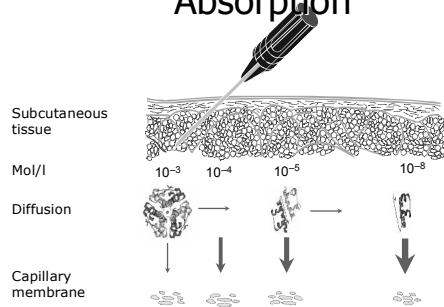


Self-association of Insulin: Monomer -> dimer -> hexamer



Whittingham JL *et al. Biochemistry* 1998;37:11516-11523.

Insulin Aggregation and S.C. Absorption



Adapted from Brange, *Diabetes Care* 1990;13:923-954.

Insulin Analogues?

- Insulin regimens should:
 - mimic insulin profiles of healthy individuals (post-prandial spikes & basal levels)
 - Maintain effective glycaemic control and avoid complications
- Novel modifications needed to:
 - Change duration
 - Change action
 - Prevent nocturnal hypoglycemia

Gummerson, I. Insulin analogues revisited. *Hospital Pharmacist*: 2003(10) : 165 - 172

Insulin Pharmacodynamics

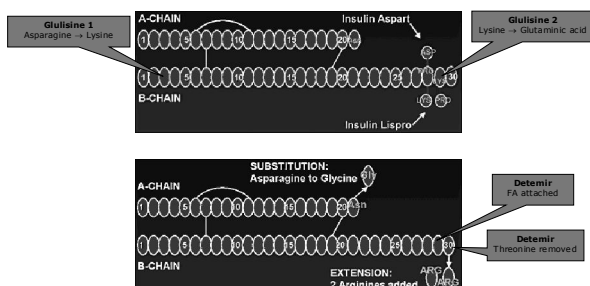
| Insulin | Onset (hr) | Peak (hr) | Duration (hr) | |
|-------------------|---------------|-----------|---------------|--------|
| Insulin Lispro | within 15 min | ½-1½ | 3-5 | Clear |
| Insulin Aspart | within 15 min | 1-3 | 3-5 | Clear |
| Insulin Glulisine | 0.25-0.5 | 0.5-1 | 4 | Clear |
| Regular | 0.5-1 | 2-4 | 5-8 | Clear |
| NPH | 1-2 | 4-10 | 14+ | Cloudy |
| Insulin Detemir | 3-4 | 6-8 | 6-23 | Clear |
| Insulin Glargine | 1.5 | flat | 24 | Clear |
| Lispro Mix 50/50 | 0.25-0.5 | 0.5-3 | 14-24 | Cloudy |
| Lispro Mix 75/25 | 0.25-0.5 | 0.5-2.5 | 14-24 | Cloudy |
| Aspart Mix 70/30 | 0.1-0.2 | 1-4 | 18-24 | Cloudy |

International labeling

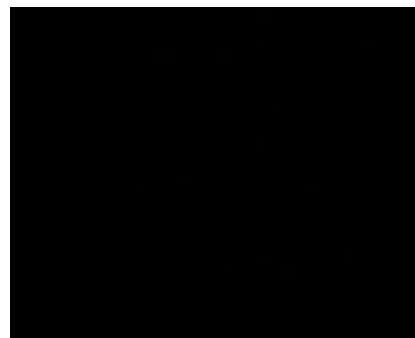
| Product Group | Product | Colour Name | Pantone Colour No. | Colour |
|--------------------------------|----------------------|-------------|--------------------|--------|
| Fast acting insulin | Regular | Yellow | 123C | |
| | Regular Buffered | Red | 185C | |
| | Hoechst Pump Insulin | Blue | 072C | |
| Insulin Mixtures (Regular/NPH) | 50/50 | Grey | 445C | |
| | 40/60 | Violet | 253C | |
| | 30/70 | Brown | 471C | |
| | 25/75 | Turquoise | 313C | |
| | 20/80 | Magenta | Magenta C | |
| | 15/85 | Olive | 104C | |
| | 10/90 | Blue-Green | 328C | |
| Long acting insulin | NPH | Light Green | 375C | |
| | Lente | Turquoise | 312C | |
| | Ultralente | Dark Green | 363C | |
| | Similente | Light Blue | 545C | |

www.idf.org

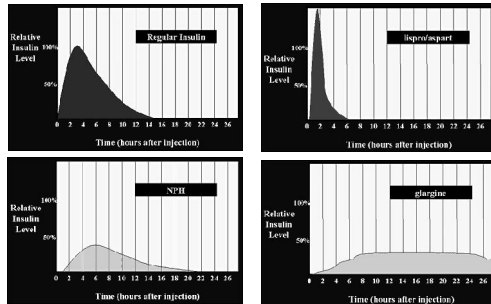
Synthetic Insulin



Insulin action (Detemir)



Insulin Pharmacokinetics



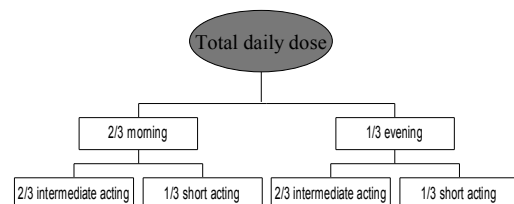
Treatment Strategies

- Most patients require an insulin dosage of 0.5 – 1.0 U/kg daily
- Athletes and patients near their ideal body weight generally require less insulin than obese patients and those leading a sedentary lifestyle
- Be aware of the honeymoon period
- Constantly reassess and adjust the insulin dose until the patient stabilizes

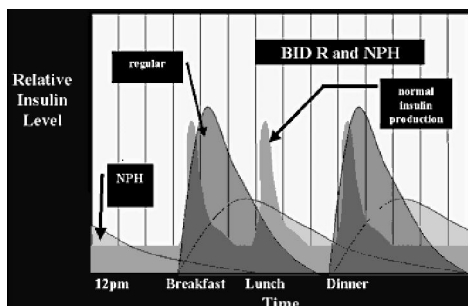
Insulin Regimens

- Traditional once or twice daily injections
 - No longer recommended
 - Still appropriate in many cases
 - # Initial therapy
 - # Patients with poor understanding of the disease
- Flexible diabetes therapy
 - Basal
 - Meal time
 - # require a intelligent and motivated patient
 - # 4 injections needed daily

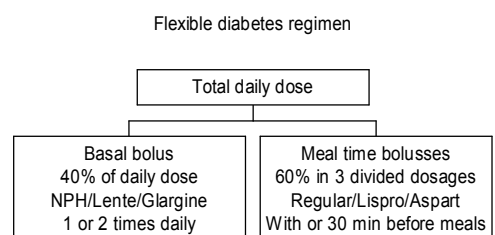
Twice Daily Regimen



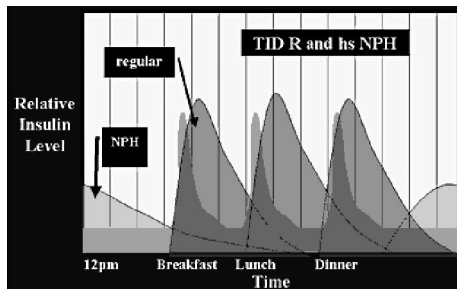
Twice Daily Regimen



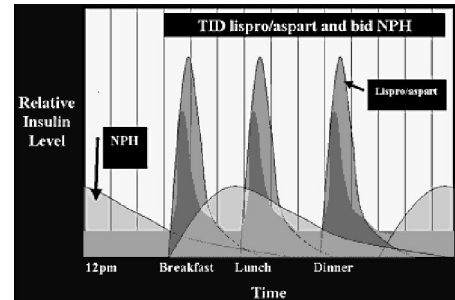
Flexible Diabetes Therapy



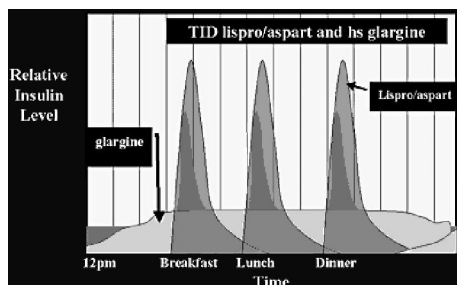
Regular Insulin and NPH



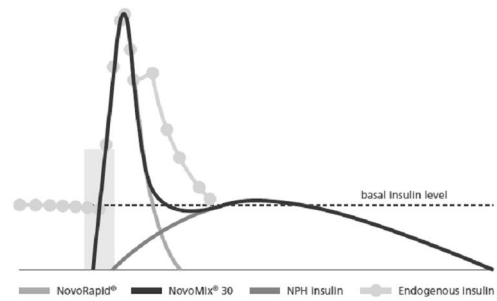
Lispro/Aspart/Glulisine and NPH



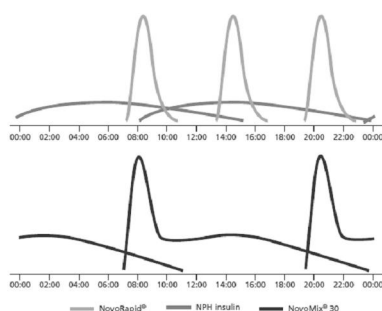
Lispro/Aspart/Glulisine and Glargine



Premixed Analogues



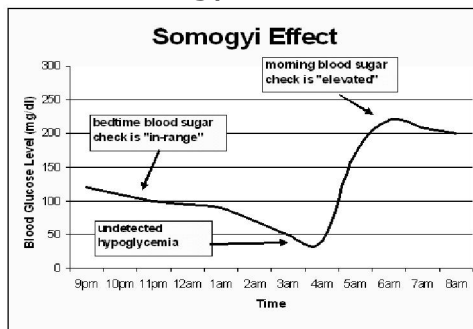
Premixed Analogues



Insulin supplementation

| Insulin Supplementation – Regular insulin | | | | | |
|---|--------------------------------|---------------|---------------|-----------|---------------------|
| Capillary blood Glucose level | Total daily insulin | | | | |
| | A 0 – 20U | B 21 – 46U | C 47 – 72U | D >72U | E Individualised |
| < 4 | Initiate hypoglycaemia regimen | | | | |
| 6 – 8 | + 0 | + 2 | + 4 | + 6 | |
| 8.1 – 10 | + 2 | + 4 | + 6 | + 8 | |
| 10.1 – 13 | + 4 | + 6 | + 8 | + 10 | |
| 13.1 – 17 | + 6 | + 8 | + 10 | + 12 | |
| 17.1 – 20 | + 8 | + 10 | + 12 | + 14 | |
| > 20 | + 10 | + 12 | + 14 | + 16 | |

Somogyi vs Dawn



Injecting insulin

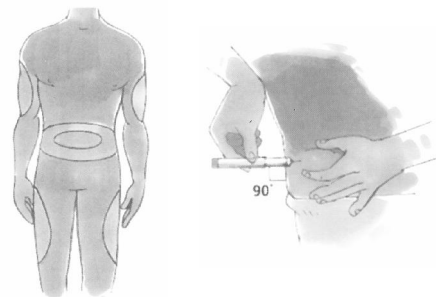
- Should be given into subcutaneous tissue
- Skin of a very thin person may have to be gently pinched
- Insulin at room temperature less painful
- Needle can be inserted at 45-90°
 - 45° for very thin people
 - 90° for overweight people or when using short needle
- Swabbing with alcohol is not necessary



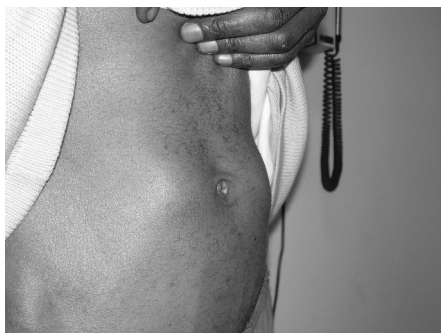
"I don't think that's what they mean by rotating injection sites, honey!"

© 2004 Diabetes Health

Injection Sites and Technique



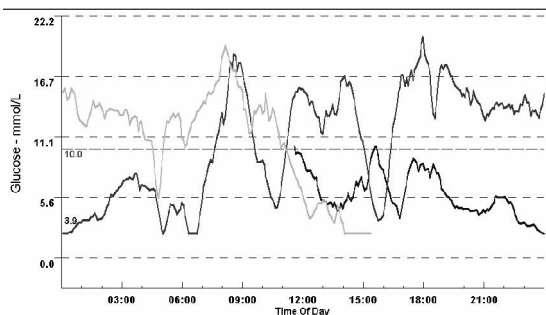
Wrong injection technique



Factors affecting absorption

- Lipohypertrophy
- Dose of injection
- Site and depth of injection
- Exercise
- Ambient and body temperature
- Insulin type
- Incomplete re-suspension

Variability in insulin absorption



Despite the valiant efforts of the research group, the insulin suppository still had one major drawback.

Initiation of Insulin



Commencing insulin therapy

- Starting dose will depend on many factors
 - age
 - weight
 - type and duration of diabetes
 - glycaemic targets
- In type 2 diabetes, consider continuing maximum tolerated oral glucose-lowering medicines
 - 10 units of intermediate-acting insulin once a day

Commencing insulin therapy

- Insulin should never be used as a threat
- Fear of injecting is common; needle phobia is rare
- Healthcare professional's attitude is key to acceptance
- People should be praised and encouraged to promote a positive attitude
- Blood test is more painful than insulin injection
- Forget the oranges; just do it!

Adjusting insulin

Pattern management

- Watch levels for 2-3 days
- Address hypoglycaemia first
- Aim for target fasting levels next
- Adjust by 2-4 units or 10%
- Wait 2-3 days

Adjusting insulin

- Flexible dose guideline
- Eating more
- Exercising more
- Insulin to carbohydrate ratio
- Evaluate with next blood glucose
- Tailored to individual needs

Which insulin to adjust when?

| Blood glucose | Insulin to be changed |
|----------------------|---|
| Fasting | Bedtime or supper intermediate- or long-acting |
| Post-breakfast | Morning short- or rapid-acting insulin |
| Pre-lunch | Morning intermediate-acting insulin |
| Post-lunch | Morning intermediate-acting insulin or lunchtime short- or rapid-acting insulin |
| Pre-supper (dinner) | Morning intermediate-acting insulin |
| Post-supper (dinner) | Supper-time short- or rapid-acting insulin |
| During the night | Supper-time or bedtime intermediate-acting |

Insulin practicalities

Timing

- Soluble insulin: 30-45 minutes pre-meal
- Short-acting insulin analogues: no more than 15 minutes pre-meal and can be given post-meal
- Intermediate- or long-acting insulins do not have to be given in relation to a meal

Insulin practicalities

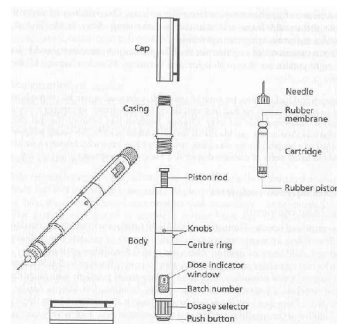
Storage

- One month in fridge or at room temperature once the vial has been opened
- Must never be frozen
- Store away from source of heat
- If refrigeration not available store in clay pot or hole in ground
- May be damaged by direct sunlight or vigorous shaking

Side effects

- Hypoglycaemia
- Weight gain
- Lipohypertrophy
- Lipoatrophy
- Insulin oedema
- Allergic reaction

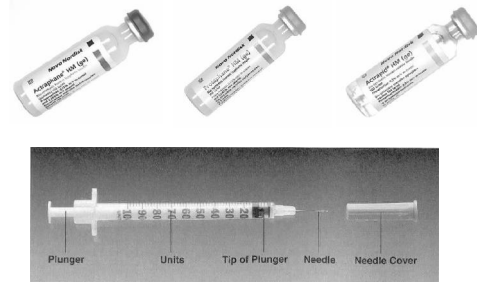
Novopen



Lilly pen



Vials and Syringes



Insulin Pumps



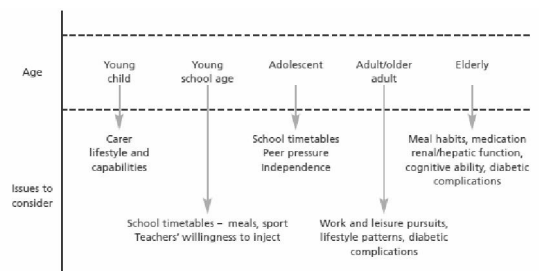
Insulin Pumps



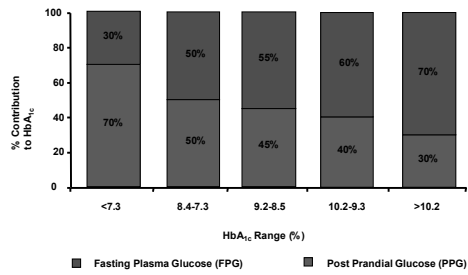
Inhalation Insulin



Insulin Regimen Adjusted to Lifestyle



Importance of Postprandial Glucose



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

Blood glucose monitoring is essential

