A/Prof Tim Kenealy

General Practitioner

South Auckland

RN Rab Burtun

Diabetes Nurse Specialist

Waitakere Hospital

Starting Insulin in General Practice Workshop - Pre-Conference Workshop

Thursday, 28 July 2011 Start 2:00pm Duration: 4 hours Greenslade Room



Breaking Down the Barriers to Insulin use

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Priority area

Glycaemic control: insulin initiation

- Shift in diabetes service delivery from secondary care to primary care
- This has followed on from implementation of the free diabetes annual review
- NZGG Diabetes Advisory Group recommended primary care be given the skills, capability and permissions to initiate insulin where appropriate
- This guidance provides practitioner support for the initiation of insulin in the primary care setting
- *Management of Type 2 Diabetes :New Zealand Guideline Group 2011.Ministry of Health*

Where do we start?????????

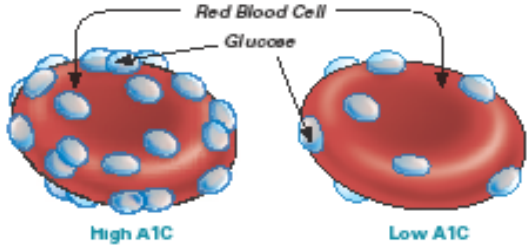
Dear Dr

- **Thank you for seeing Mr Tough guy who is a 48 yrs old builder.**
- *Type 2 for 8 yrs ,on*
- *Metformin 850 mg bd*
- *,Glipizide 10 mg bd ,Hba1c is 11.2%.*
- *Says he take his pills everyday.*
- *Does not monitor BS says he feels well.*
- *Has Hypertention ,Hyperlipedemia ,microalbuminuria, early retinopathy was found at last retinal screening.*
- *Smokes 20 cigs a day.*
- *Very reluctant to go on Insulin.*


GILBERT

How to prevent complications?

What is A1C?



Work on your A1C

American Diabetes Association. Implications of the United Kingdom prospective diabetes study. Diabetes Care 2003; 26(Suppl. 1): S28-32

1% Reduction in A1C = **35%** Reduction in risk of complications

Being in control or intensive management* can prevent diabetes-related complications

Eyes
76% reduced risk of developing retinopathy with tight control

Kidneys
34% reduced risk of developing nephropathy with tight control

Nerves
69% reduced risk of developing neuropathy at 5 years with tight control

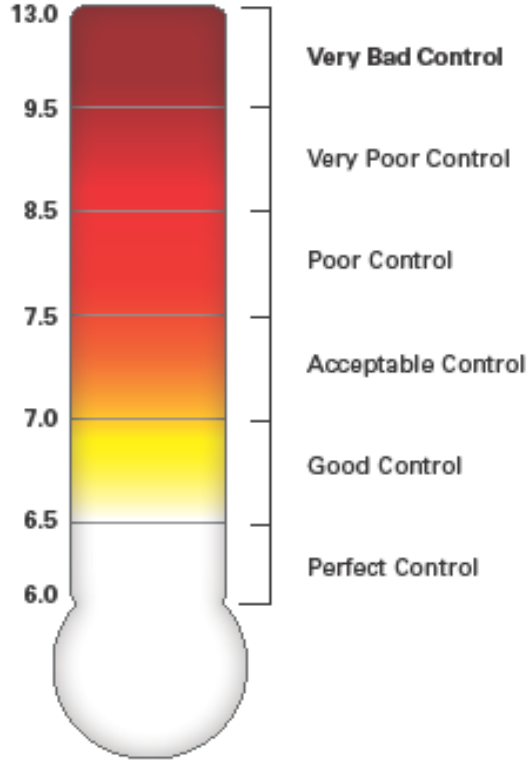
Individualise the target

DCCT % HbA_1C		IFCC Mmol/mol		
6 - 6.5%	→	42 - 48	→	Too low (if on insulin or sulph.)
6.5 - 7%	→	48 - 53	→	Excellent
7 - 8%	→	53 - 64	→	Good
8 - 9%	→	64 - 75	→	Bit high
9 - 10%	→	75 - 86	→	Too high
10+%	→	86 and above	→	Urgent. Attention needed

To work out DCCT % HbA_1C in IFCC Mmol/mol: -2 – 2 rule
i.e: HbA_1C of 7% = 7 – 2= 5 – 2 = 3 Therefore is 53

Diabetic Control

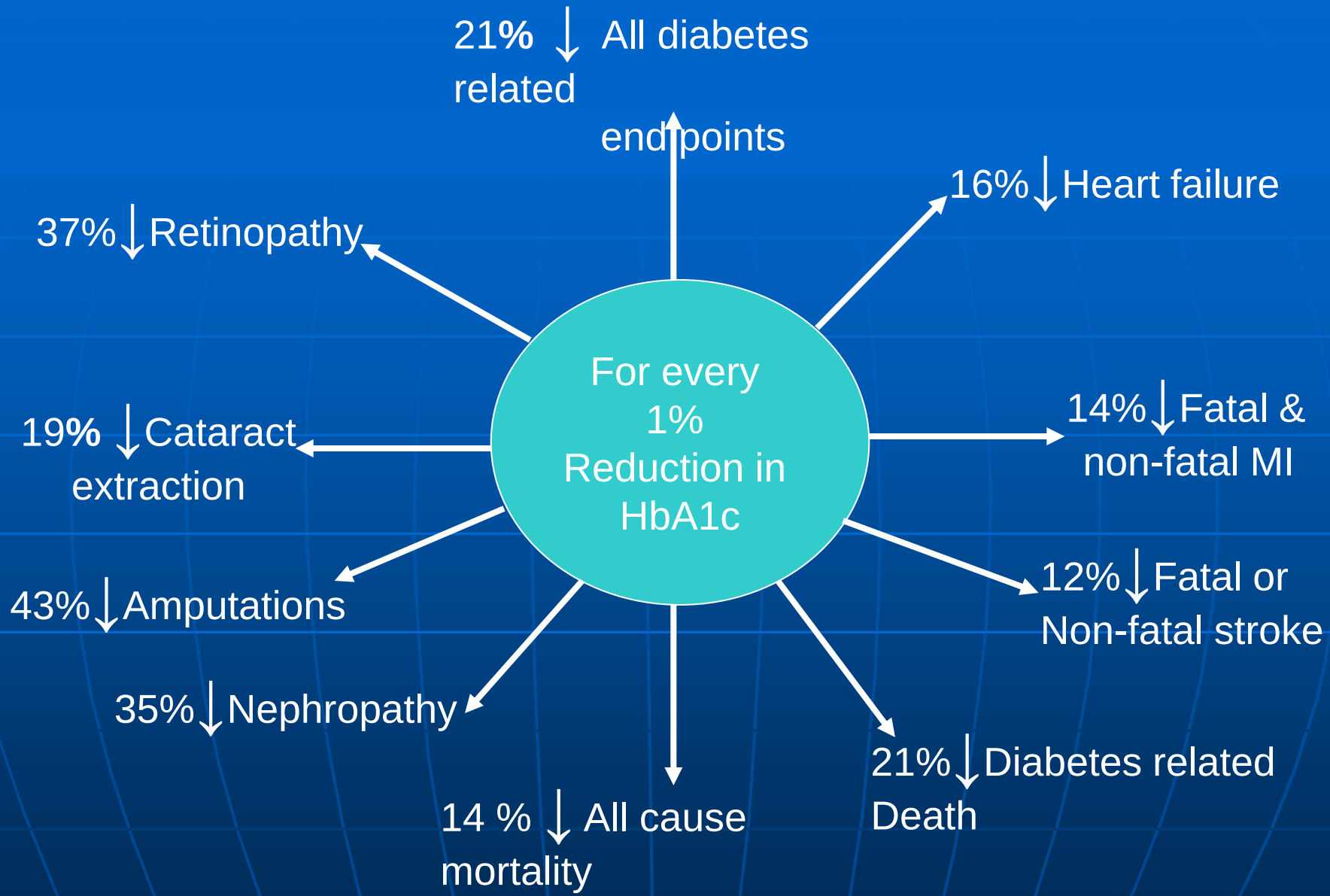
HbA_1C Thermometer



This is the best test of overall diabetic control.
The target for everyone is less than 7%.
If your result is 8% or more, please contact your nurse or doctor.

N.B. Target for pregnant diabetics is less than 6.5%

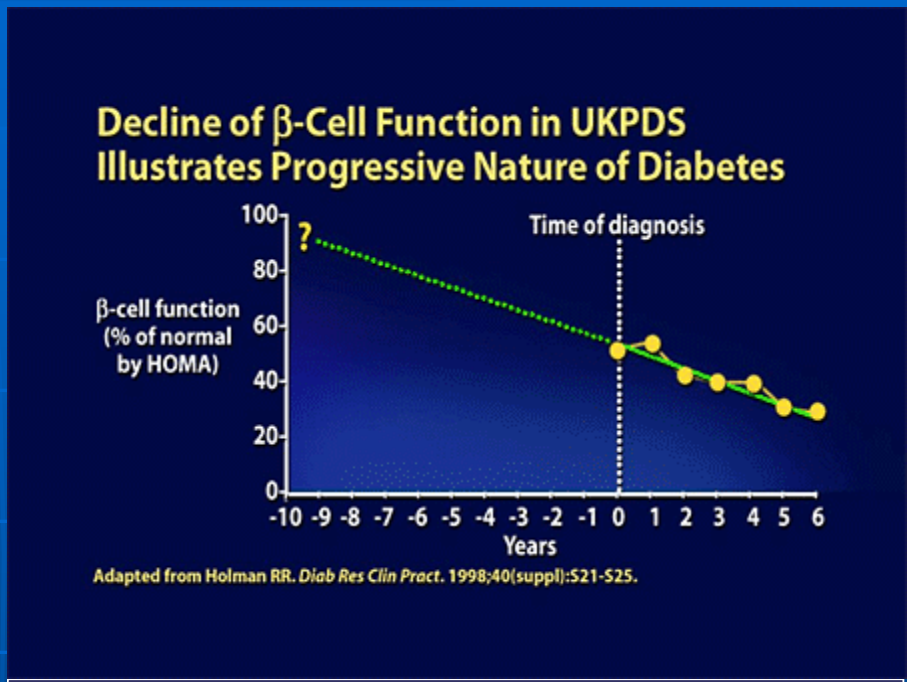
Insulin Leadership Summit



Stratton IM, Adler AI, Andrew H, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS35): prospective observational study. British Medical Journal 2000; 321: 405-1.1

Progressive nature of Diabetes

- *Before insulin initiation, patients may have spent an average of about 5 years with an A1C >8% and nearly 10 years >7%*
- *At diagnosis, up to 50% of a patient's β-cell function may have been lost, and may continue to decline by about 4% annually*
- *Remind patients that diabetes is a progressive disease and that their treatment plans may be adjusted over time. An overall treatment plan to lower A1C consists of diet, exercise, and diabetes medication, which may include insulin.*
- *50% of Type 2 needs to go on Insulin within 7 yrs (UKPDS)*
- *Let patients know fear of insulin is not uncommon. Help them understand the facts about insulin therapy*



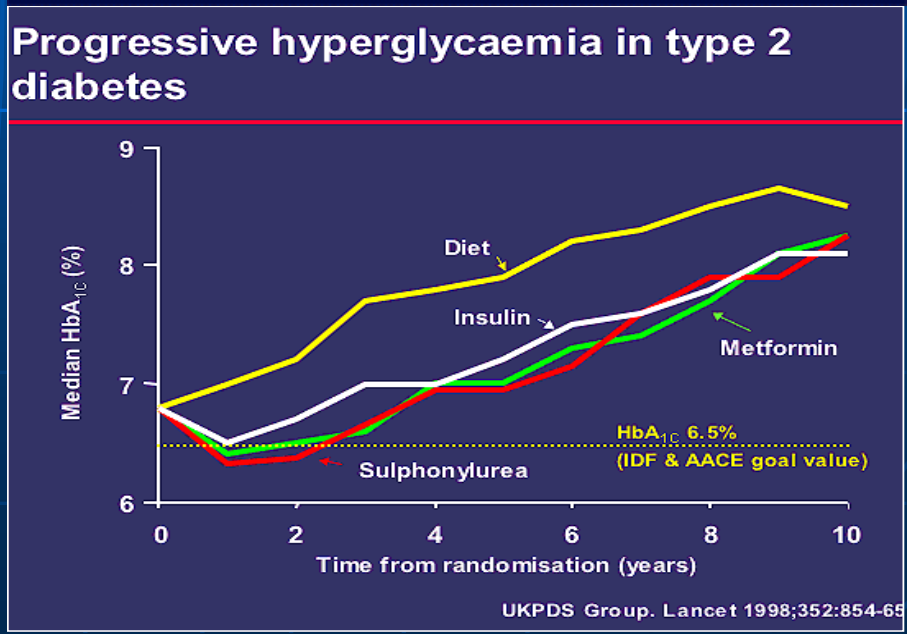
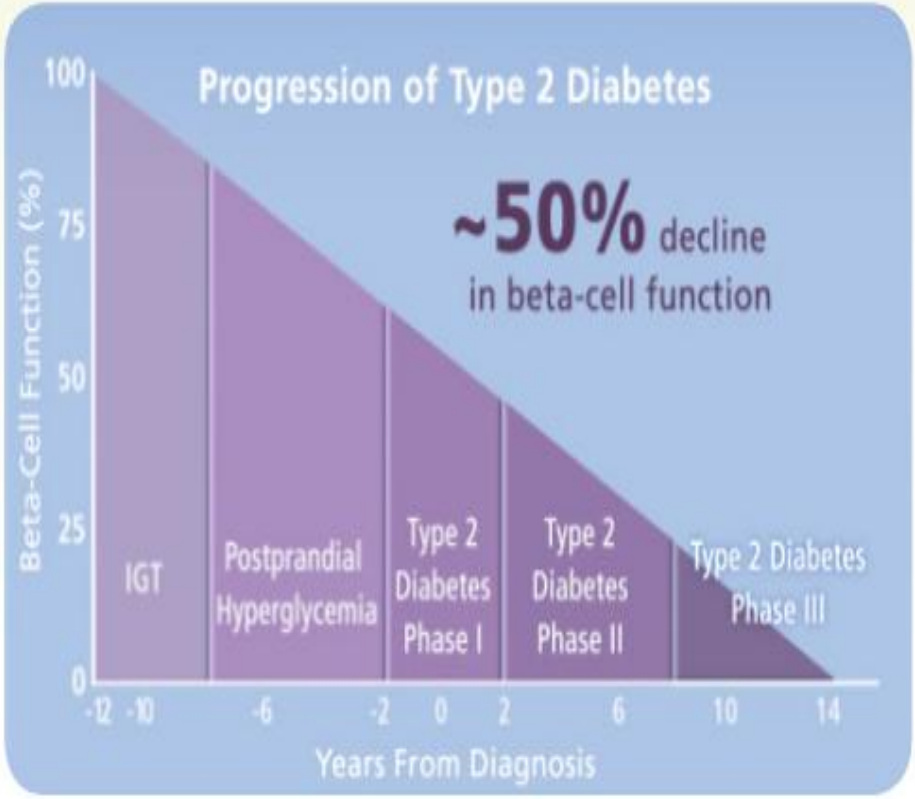
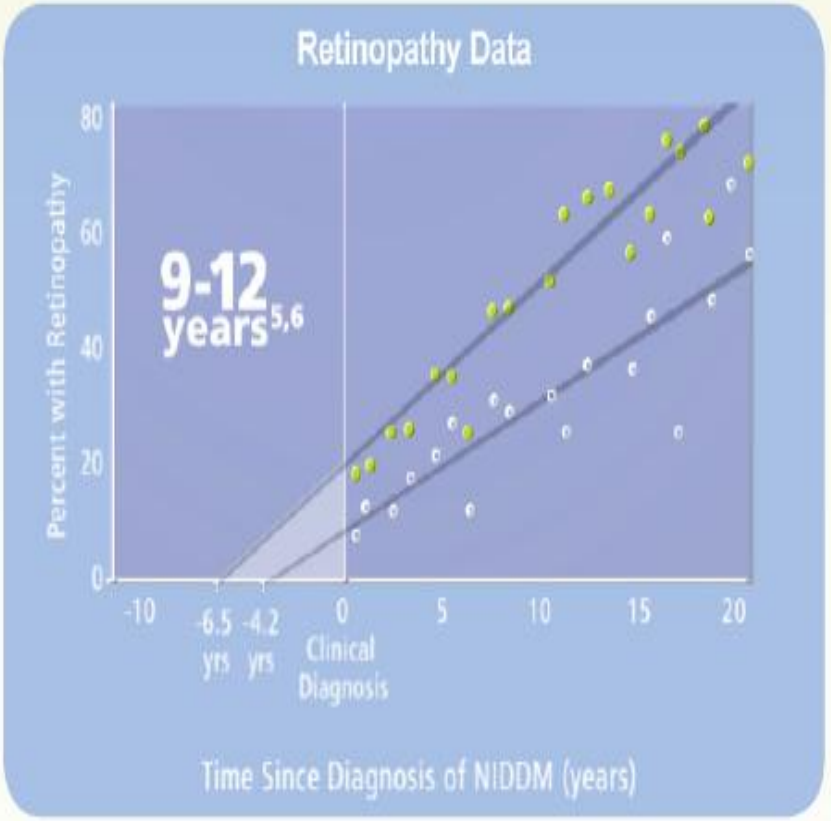


Fig. 1: **Beta-cell function in type 2 diabetes mellitus**



Data from a subset of patients in the United Kingdom Prospective Diabetes Study (UKPDS). Beta-cell function was estimated by homeostasis model assessment (HOMA) model at diagnosis (0) and over 6 years. Data were extrapolated backward to estimated 100% beta-cell function and forward to expected lack of significant insulin secretion. Adapted from Lebovitz.[2]

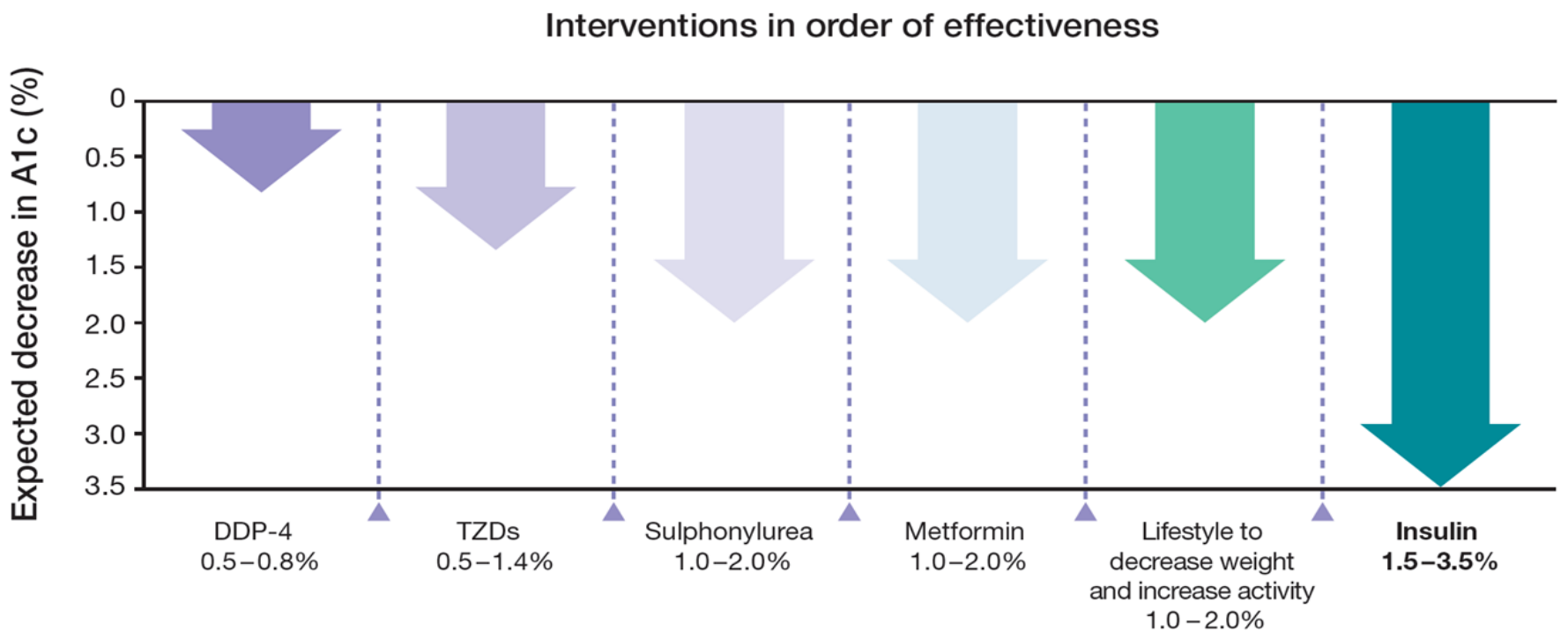
Fig. 2: **Retinopathy may begin before diagnosis**



Results from a cross-sectional analysis of retinopathy prevalence and time since diagnosis in two population-based subgroups of adult patients with type 2 diabetes (N=2070). A weighted linear regression was performed to evaluate the relationship between retinopathy prevalence and duration of disease. Lines were extrapolated backward to estimated onset of retinopathy. Adapted from Harris et al.[5]

Insulin-the most effective intervention[3]

A1c lowering potential of individual therapeutic options[2]



Adapted from Nathan *et al.*, 2009. DDP-4 = Dipeptidyl peptidase-4 inhibitor. TZDs = Thiazolidinedione.

Barriers to Insulin Therapy

Patient Factors

- Weight gain
- Social embarrassment
- Fear of hypoglycemia
- Lifestyle changes
- Painful injections
- Feelings of failure/guilt
- Becoming more ill; disease progression

Physician Factors

- Fear of patients' anger and alienation; losing patients
- Concern over compliance
- Burden of additional training or dealing with crises during transition
- Hypoglycemia
- Weight gain

Korytkowski M. *Int J Obesity*. 2002;26(Suppl 3):S18-24.

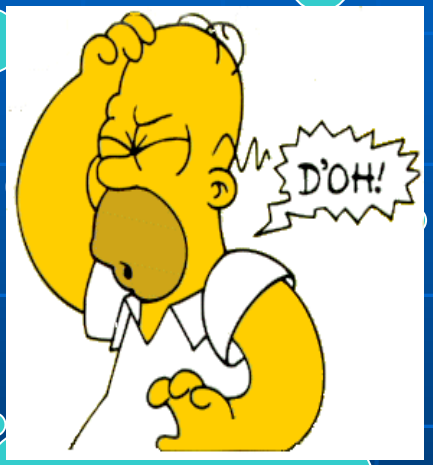
Many factors contributes to fears of insulin!!

Cost? the pen looks nice and expensive! !can I afford that??

Disease getting worst!! Some people have morphine injections when they are about to die!

Hypoglycaemia!!. Seen friend or neighbour call ambulance!! Fitting!! Was scary!!

Pain!!does it go into a vein??Seen it on TV Huge needle and drug addicts have to find a vein!!Too complicated!!



Its forever!! Addiction?? Once you on it you stay on it ?? Cultural beliefs :is it from pigs/Cow

Lifestyle change!!

Travel/work/beer?? Will I still be able to go out and have sweets puddings etc??

Insulin causes complications!!Aunty Nelly was well into herv 80s until she went on Insulin she was dead after 3 months on Insulin

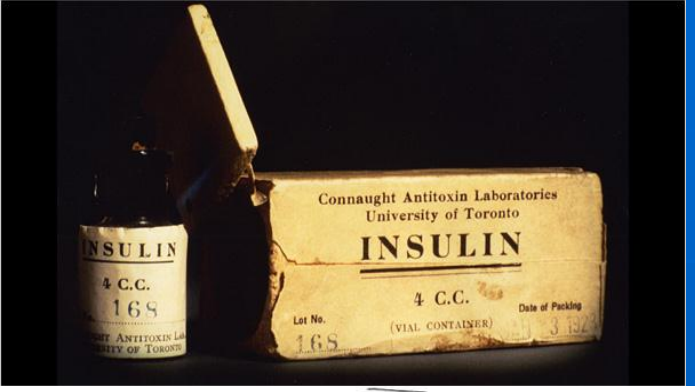
Personal failure!!I am a loser !!why I cant beat this ??!!Why have I failed???

Barriers to insulin therapy often come from common fears and misperceptions. Some ways to help address these issues are outlined below.

- **Disease getting worse???**
- *Inform patients that blood glucose may rise over time*
- *Reassure patients that it may not be entirely their fault. The increasing inability of the pancreas to produce enough insulin may be the main reason for disease progression*
- **Hypoglycemia????**
- *Some people are concerned about side effects, such as hypoglycemia.*
- *Acknowledge that hypoglycemia is the most common side effect of insulin*
- *Advise patients taking insulin to regularly check their blood glucose*
- *Teach patients how to recognize and treat hypoglycemia, should an episode occur*
- *Inform patients of the common things that can affect their blood glucose levels, such as medications, changes in food intake, illness, physical activity and stress*
- **It's forever????**
- *Many patients have concerns about chronic use of insulin.*
- *Assure patients that insulin is not physically addictive or habit-forming*
- *Inform patients that you may adjust their insulin doses upwards or downwards over the course of their treatment to assure they are on the proper dose*
- **Why not try it for a month???**

Continued!!

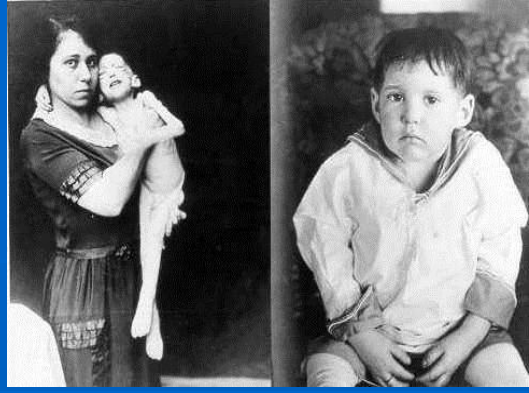
- **Failure??**
- *Reframe the perception of failure and self-blame.*
- *Educate patients that insulin helps to replace what the body isn't adequately making to lower blood glucose*
- *Remind your patients that insulin may be an appropriate choice for them since it is effective at lowering A1C when added to an overall treatment plan*
- *Educate patients about what they can do by making healthy food choices and increasing their physical activity .Address problem of SNACKS or eating in between meals ??????*
- **Lifestyle change**
  Many patients believe that taking insulin will greatly disrupt their lives.
- *Inform patients that insulin may help control blood glucose and lower A1C1*
- *Present insulin as another effective option to add to their daily diabetes management routine*
- *Patients may find that insulin can become a normal part of their routine*
- **Pain**
  If fear of pain is deterring your patient from taking insulin, consider the following:
- *Insulin is injected in the fatty layer just under the skin where there are fewer nerve endings and injections generally cause little discomfort*
- *Tell patients that many people on insulin are surprised by how soon they get used to the injections*
- **Get Partner or Friend ,parent or Children to try needle first!**
- **Provide information about insulin benefits, Would sleep better, have more energy, not feel constantly tired, mood, thirsty, thrush in women!!!, improve erectile dysfunction in men!!!!!**



Insulin is Good for you !!!!

Insulin is amazing!!!!!

Insulin is wonderful!!!



Soon after its discovery, insulin captivated media attention (Banting Digital Library)

DAUGHTER OF U.S. SECRETARY OF STATE TRIES NEW TORONTO DISCOVERY.
On the left is Mrs. Charles Evans Hughes, who accompanied her daughter to Toronto this week to take a new treatment for diabetes, which has been worked out at the University of Toronto. In the centre is her fifteen-year-old daughter, who is here to take the treatm ent. On the right is Dr. F. G. Banting, 160 Bloor street west, who is the originator of the insulin treatment for diabetes, and who for over a year has been doing research work along with Mr. C. H. Best, of Toronto. The new treatment has already prolonged the lives of many sufferers from the disease.

Every few months some miracle drug or other is rolled out with bells and confetti, but only once or twice in a generation does the real thing come along!!!!

<u>These are the blockbuster medications that can virtually raise the dead</u>…., *Insulin was one of them….. Insulin actually put flesh on living skeletons. With insulin, dying children laughed and played again, as parents wept and doctors spoke of biblical resurrections..... mothers all over the globe were writing him heart-wrenching letters: "My dear Dr. Banting: I am very anxious to know more of your discovery," wrote one, going on to describe her daughter's case: "She is pitifully depleted and reduced……"*

Normal Insulin Profiles

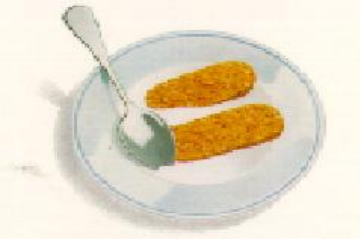
the body needs a constant level of sugar in the blood

the blood sugar rises

and a background level of insulin

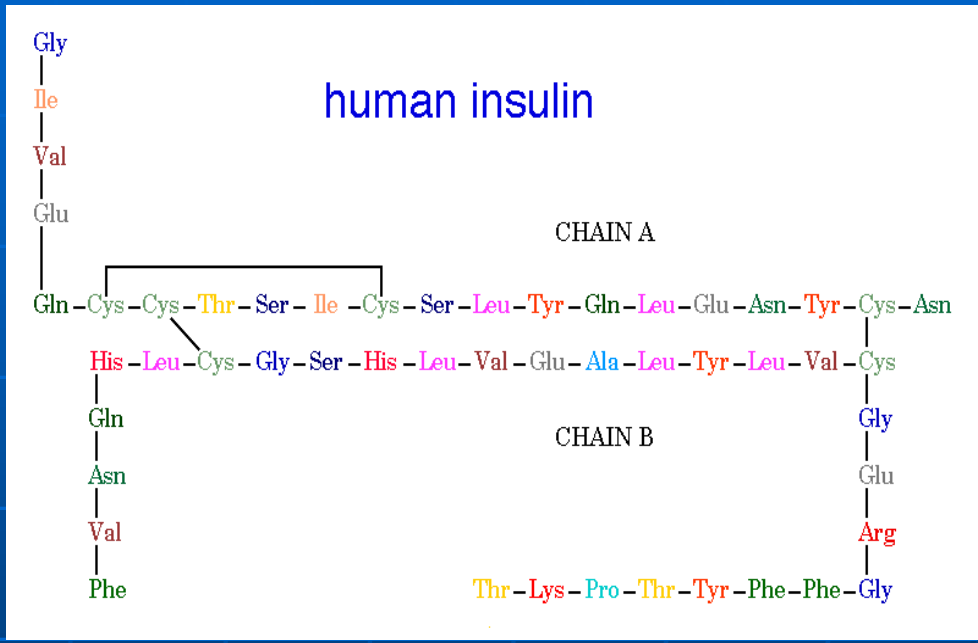
and extra insulin is needed

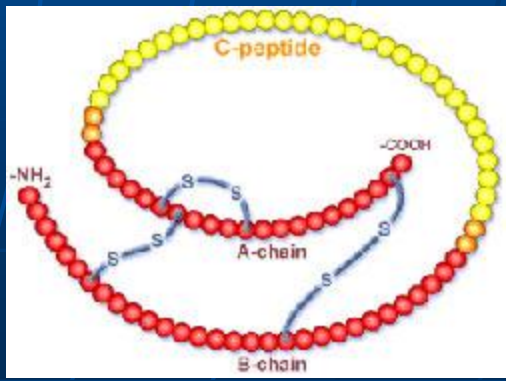
Normal Insulin Profiles



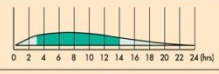
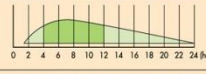
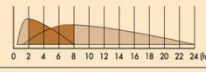
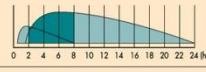
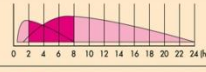
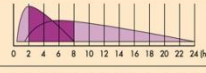
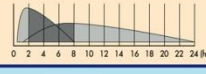
Types of Insulin

- Short acting
- Intermediate acting
- Long acting
- Biphasic
- Analogue Mixtures
- Short Acting Analogues
- Long acting Analogues





NOVO NORDISK - BALANCING INSULIN AND DELIVERY.

Brand	Presentation	Schematic Time-Action Profile*	Insulin Profile*
NovoRapid® *Rapid-acting insulin aspart (rys)*	3mL **Penfill®** 10mL Vial		Onset: 10-20 minutes Peak: 1-3 hours Duration: 3-5 hours
Levemir® *Long-acting insulin detemir (rys)*	**FlexPen®**		Peak: 3-14 hours Duration: Up to 24 hours
Actrapid® *Short-acting human insulin (rys)*	3mL **Penfill®** 10mL Vial		Onset: 30 minutes Peak: 1-3 hours Duration: 8 hours
Protaphane® *Intermediate-acting human insulin (rys)*	3mL **Penfill®** 10mL Vial		Onset: 1.5 hours Peak: 4-12 hours Duration: 24 hours
PenMix® 30 & Mixtard® 30 (10mL) *30% Short-acting & 70% Intermediate-acting human insulin (rys)*	3mL **Penfill®** 10mL Vial		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 10 *10% Short-acting & 90% Intermediate-acting human insulin (rys)*	3mL **Penfill®**		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 20 *20% Short-acting & 80% Intermediate-acting human insulin (rys)*	3mL **Penfill®**		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 40 *40% Short-acting & 60% Intermediate-acting human insulin (rys)*	3mL **Penfill®**		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 50 & Mixtard® 50 (10mL) *50% Short-acting & 50% Intermediate-acting human insulin (rys)*	3mL **Penfill®** 10mL Vial		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours

Please review Data Sheet before prescribing. Full Data Sheet is available from the Novo Nordisk Customer Care Centre 0800 733 737. *In clinical practice, the duration of insulin action may be shorter or longer than the durations specified. Variations between and within patients may occur depending upon injection site and technique, insulin dosage, as well as diet and exercise. ® Registered trademark of Novo Nordisk A/S. Novo Nordisk Pharmaceuticals Ltd, PO Box 51268 Pakuranga, Auckland. www.novonordisk.co.nz

Novo Nordisk Customer Care Centre
0800 733 737
www.novonordisk.co.nz

novo nordisk®

sanofi aventis
Because health matters

Lilly Insulin Range†

FULL RANGE NOW FUNDED*

Brand Name†,‡	Type of Insulin (generic name) / Product Description	Presentation	Schematic Action Profile*
Humalog®	insulin lispro Rbe RAPID-ACTING	10mL vials and 3mL cartridges	Onset: 0–15 mins Peak: 1 hour Duration: 3.5–4.5 hours
Humulin® R	insulin neutral (Soluble) SHORT-ACTING	10mL vials and 3mL cartridges	Onset: 30 mins Peak: 2–4 hours Duration: 6–8 hours
Humulin® NPH	isophane (NPH) INTERMEDIATE ACTING	10mL vials and 3mL cartridges	Onset: 1 hour Peak: 4–10 hours Duration: 16–18 hours
Humalog® Mix25®	25% insulin lispro, 75% insulin lispro protamine suspension Rbe PREMIXED INSULIN LISPRO	3mL cartridges	Onset: 0–15 mins Peak: 1 hour Duration: 16–18 hours
Humalog® Mix50®	50% insulin lispro, 50% insulin lispro protamine suspension Rbe PREMIXED INSULIN LISPRO	3mL cartridges	Onset: 0–15 mins Peak: 2 hour Duration: 16–18 hours
Humulin® 30/70	30% insulin neutral, 70% isophane (NPH) PREMIXED INSULIN	10mL vials and 3mL cartridges	Onset: More rapid than NPH alone Peak: 2–12 hours Duration: 16–18 hours

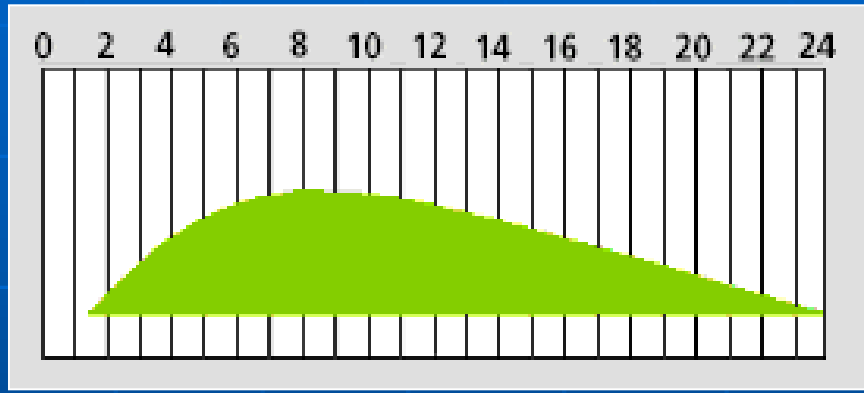
HUMAPEN LUXURA CAN ONLY BE USED WITH LILLY 3mL INSULIN CARTRIDGES. BEFORE PRESCRIBING PLEASE REVIEW THE PRODUCT DATA SHEET.

HumaPen® LUXURA

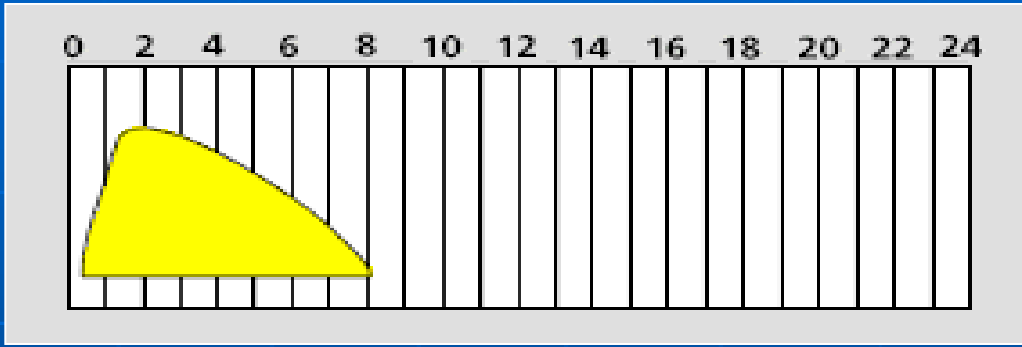
Lilly

Time Action Profiles

- Insulin/glucose levels in the blood
- Stylized format showing
  - Onset
  - Peak
  - Duration
- Intended as a guide ONLY



Short Acting Insulin Actrapid or Humilin R

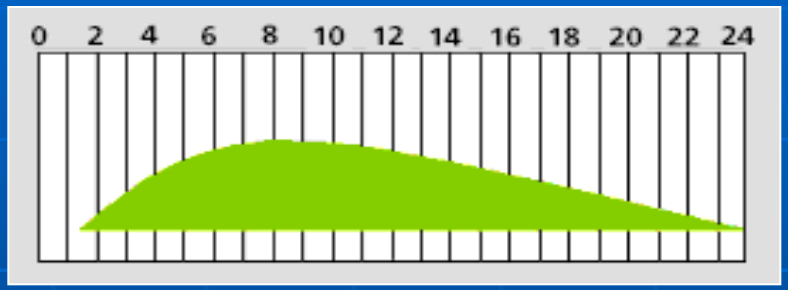


- Soluble
- Clear
- Onset 30 minutes
- Peak 1 - 3 hours
- Duration up to 8 hours

Prandial Insulin

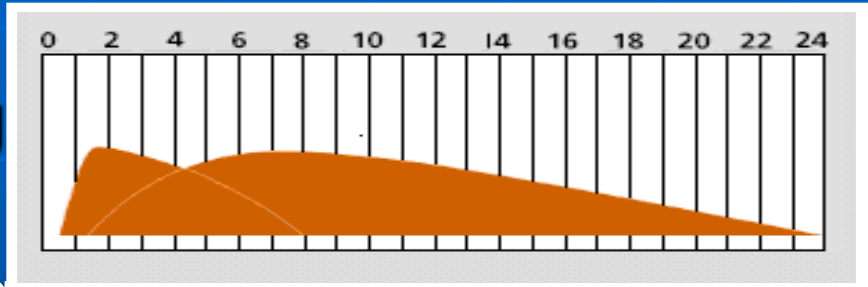
Intermediate Acting Insulin Protaphane or Humulin NPH

- Crystals in suspension (need re-suspending)
- Cloudy
- NPH (Humilin I)or Protophane (**NPH** = **N**eutral **P**rotamine **Hagedorn**)
- Onset 1 $^{1}/_{2}$ hours
- Peak 4 - 10 hours
- Duration 16 to 18 hours



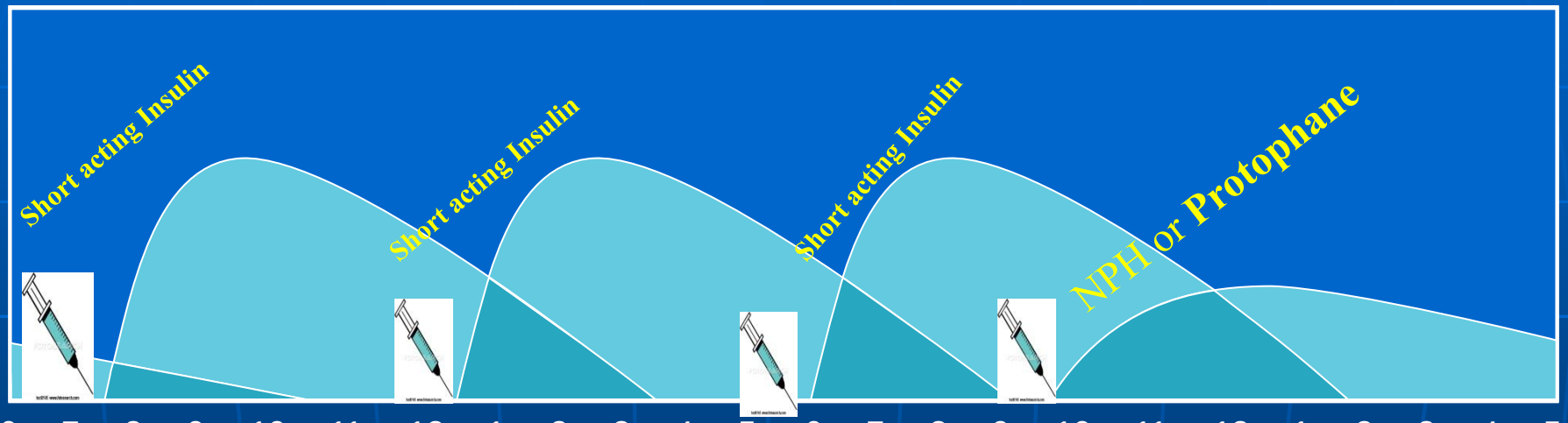
Premixed Insulins/ Biphasic Insulins

Humilin 30/70(lilly) or Penmix 30/70(Novo Nordisk)



- Pre-mixed combinations of short and intermediate acting insulins (biphasic)
- Cloudy (needs re-suspending)
- 5 different combinations (30, 40, 50)
  - e.g. 30/70 Mixture = 30% fast acting
    + 70% intermediate acting
  - **Onset 30 minutes**
- Peak 2 - 8 hours
- Duration up to 24 hours

4 Injections Per Day
3 Short + 1 Intermediate Acting
(Basal Bolus)
using Actrapid and Protaphane or Humulin R and NPH




Breakfast


Lunch


Evening Meal


Sleep

Need for Insulin Analogues

Current insulin time action profiles not ideal

- Disadvantages of existing insulins:

Short acting

- • must be injected up to 30 mins before meal
- • duration of action up to 8 hours/overlap

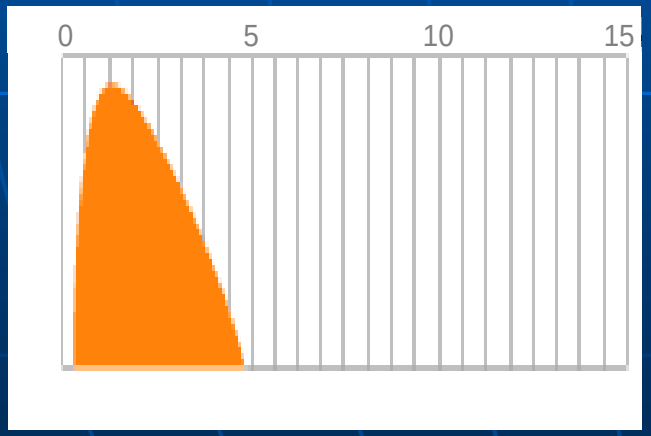
Intermediate acting

- • insulin peaks too early in night
- • increases risk of nocturnal hypoglycaemia
- • after peak, action wanes too rapidly

Rapid-acting insulins Novorapid (Insulin Aspart) NovoNordisk
Humalog(Lispro)Lilly,
Apidra (*insulin glulisine*) Aventis

- Clinical benefits
  - improved metabolic control compared with human soluble insulin
  - fewer hypoglycaemic episodes
  - no post-prandial hypoglycaemia

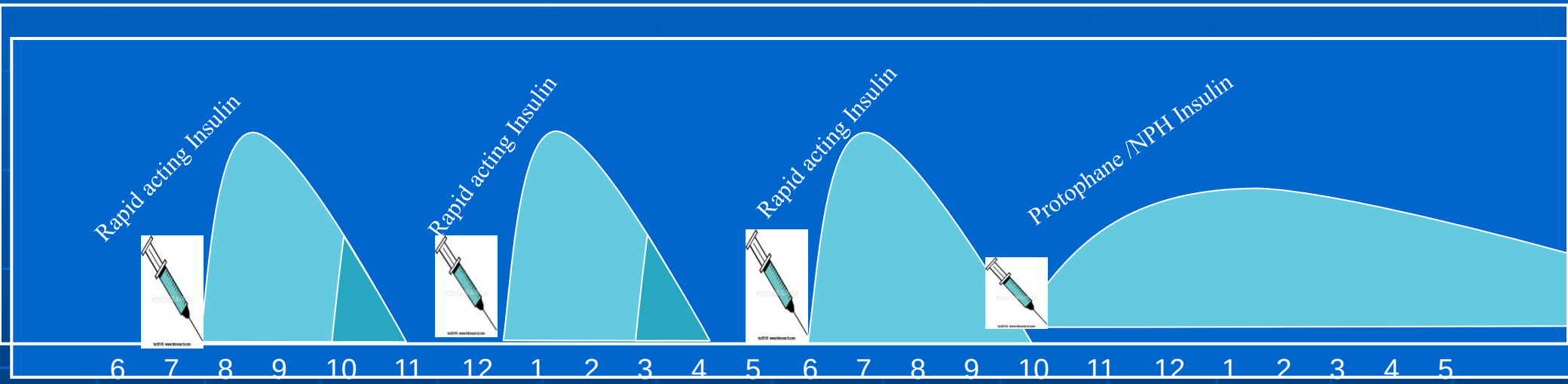
Prandial Insulins



- rapid onset of action
- short duration of action
- better quality of life and improved convenience

Onset Action : 10-20 min Peak : 1 – 3 hrs Duration : 3 – 5 hrs

4 Injections Per Day
3 rapid acting + 1 long Acting
(Basal Bolus)
Rapid Acting and Protopahne /NPH



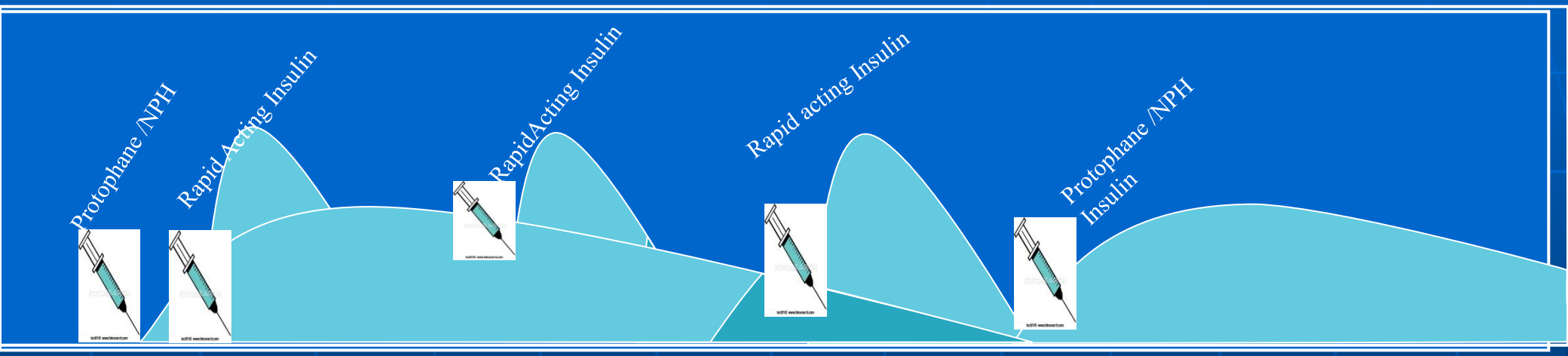
Breakfast

Lunch

Evening Meal

Sleep

4 Injections Per Day
3 rapid acting + 1 long Acting
(Basal Bolus)
Rapid Acting and Protophane or NPH BD



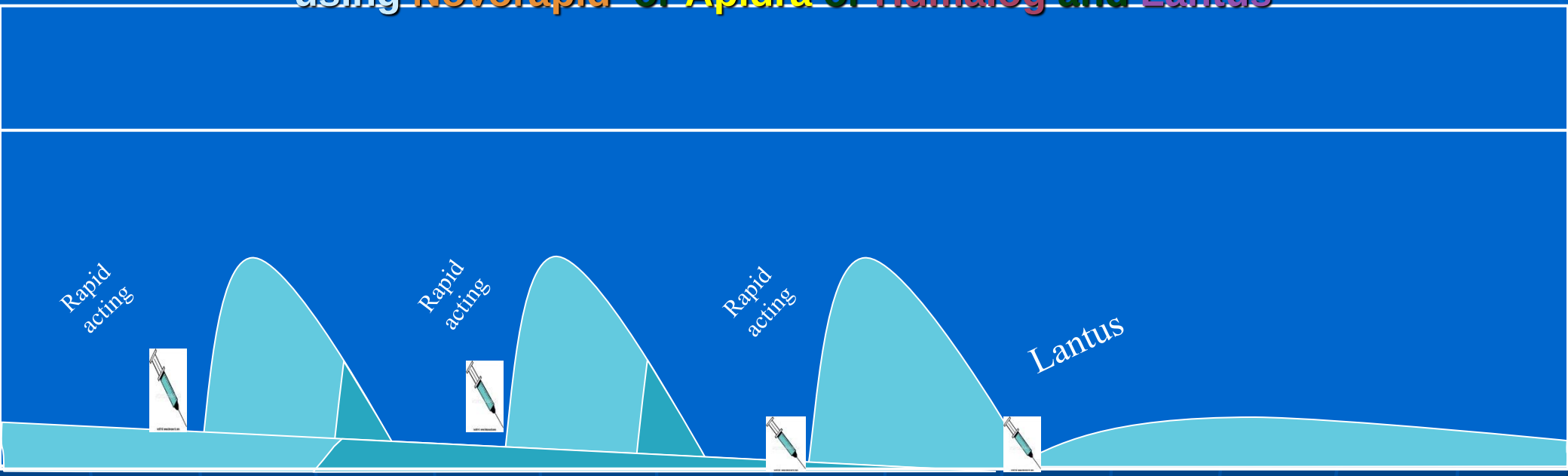
Breakfast

Lunch

Evening Meal

Sleep

4 Injections Per Day
3 rapid acting + 1 long Acting
(Basal Bolus)
using Novorapid or Apidra or Humalog and Lantus



Breakfast

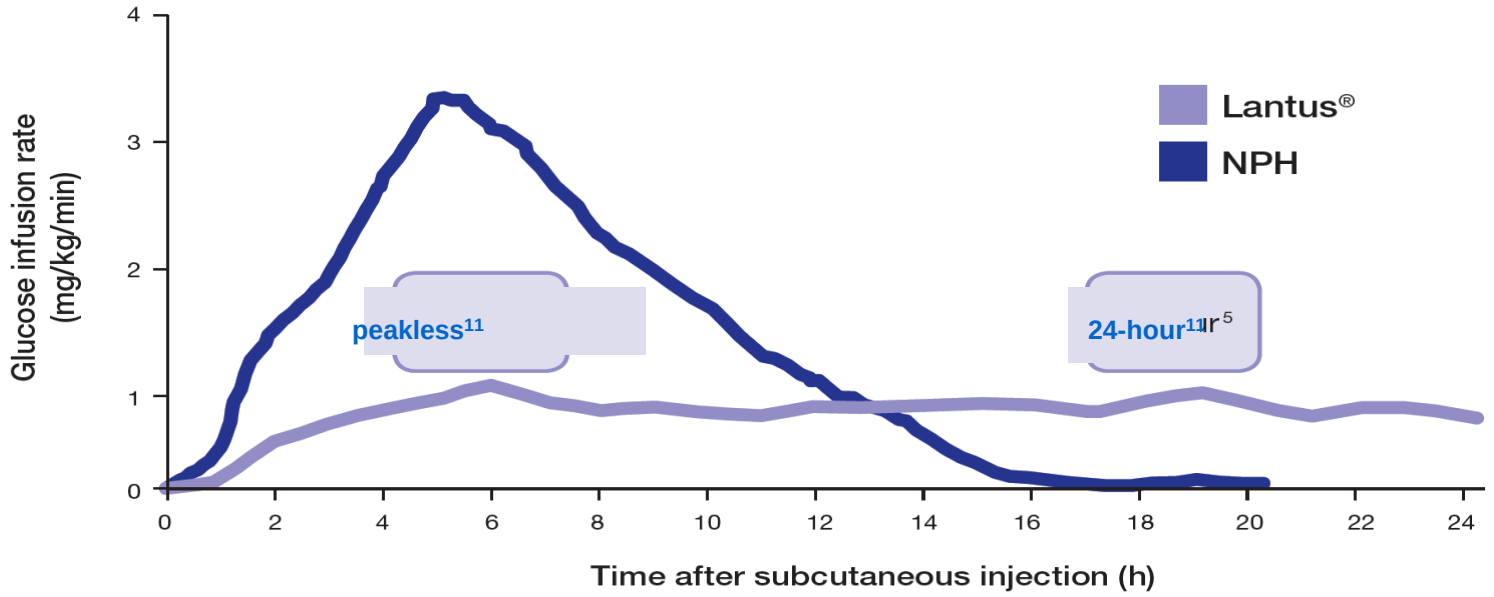
Lunch

Evening Meal

Sleep

Simple once daily dosing[4,11]

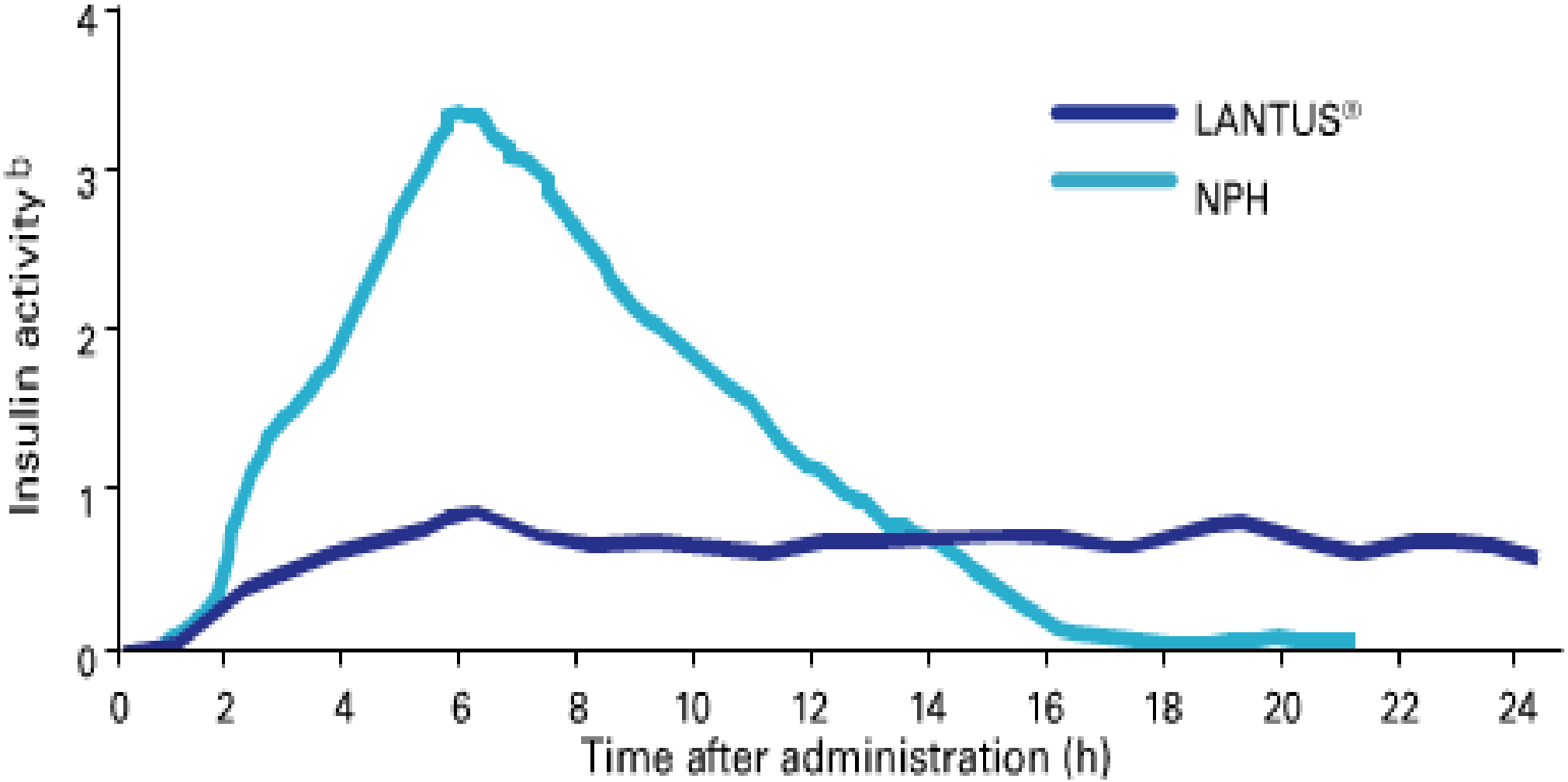
Profile of Lantus® vs. NPH[4,5] 4,11



Adapted from Lepore *et al*. 2000. Rates of glucose infusion needed to maintain target plasma glucose 7.2 mmol/L; indicative of insulin activity. Isoglycaemic clamp study in 20 C-peptide negative patients with Type 1 diabetes, crossover design testing insulin glargine and NPH at 0.3 U/kg.

LANTUS® insulin glargine

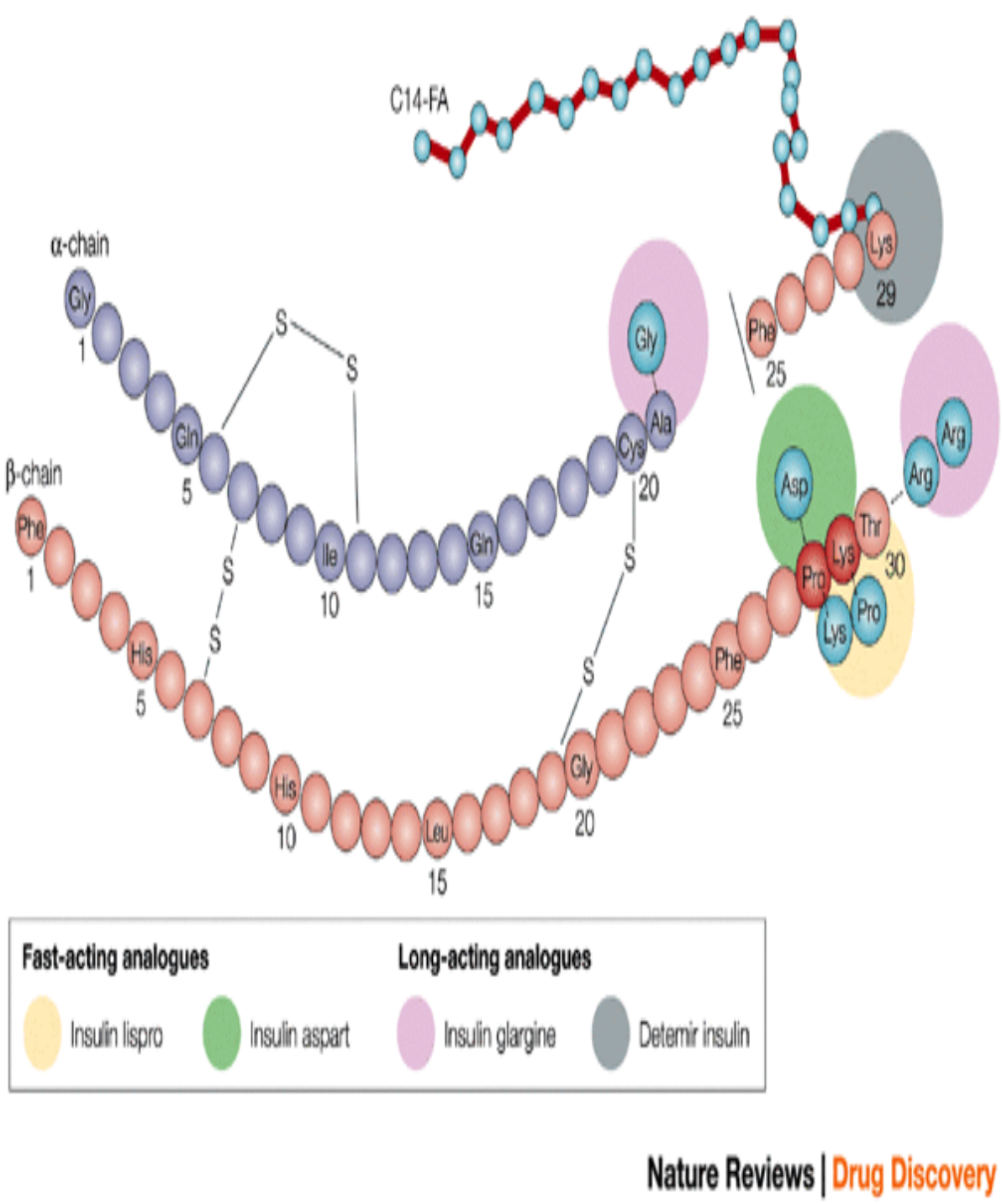
Profile of LANTUS® vs NPH in Patients with Type 1 Diabetes [a] [3, 19]

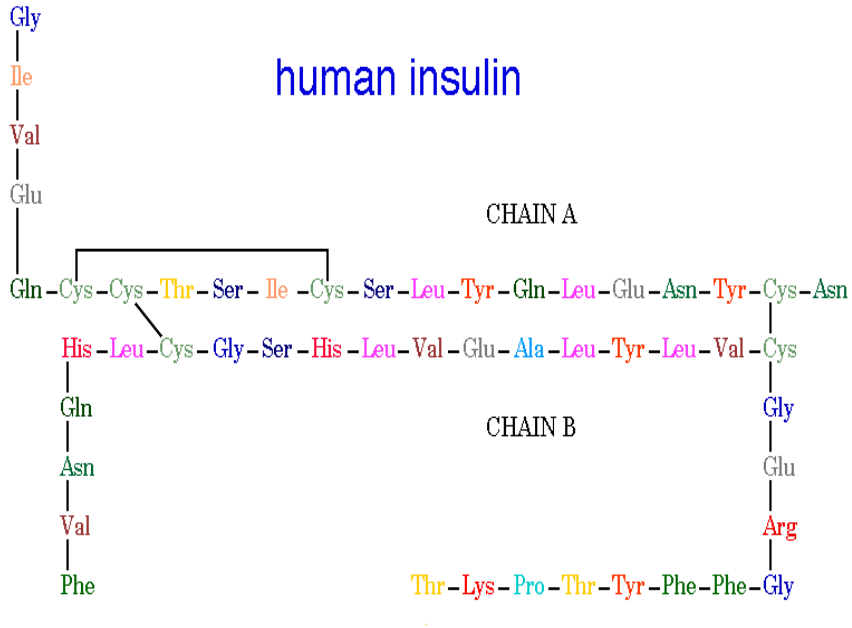


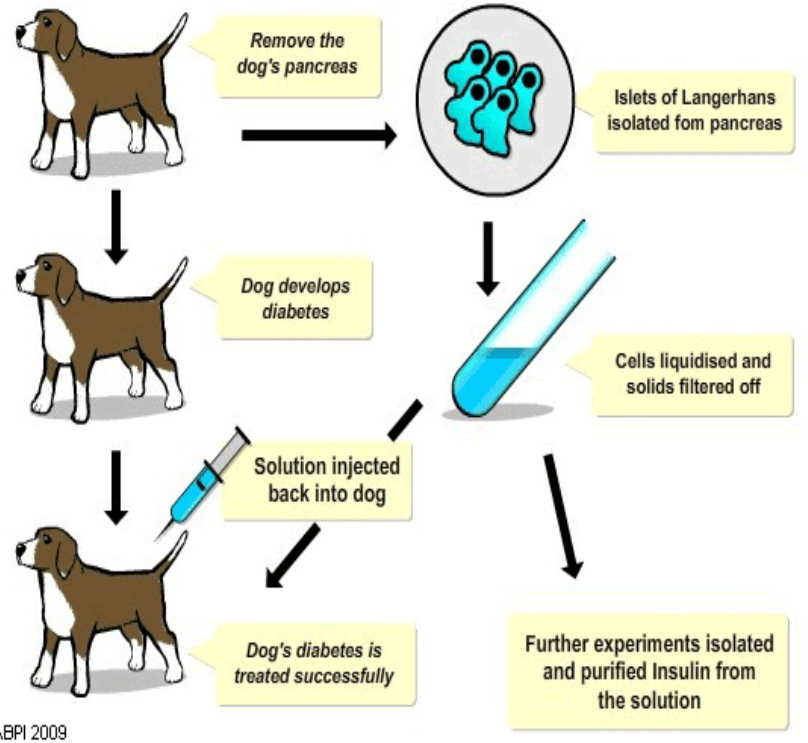
Long Acting Analogues

- Lantus

- Delayed and prolonged absorption from injection site
- Flatter profile (peak removed): Less hypos
- Longer duration of action

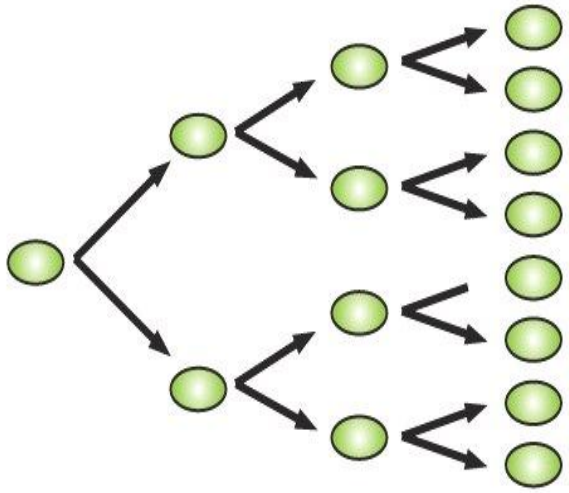

C14-FA
α-chain
β-chain
Gly
Ile
Val
Glu
Gln
Phe
His
Leu
Cys
Ala
Asp
Pro
Lys
Thr
Arg
S
1
5
10
15
20
25
29
30
Fast-acting analogues
Insulin lispro
Insulin aspart
Long-acting analogues
Insulin glargine
Determir insulin
Nature Reviews | Drug Discovery


human insulin
CHAIN A
CHAIN B
Gly
Ile
Val
Glu
Gln – Cys – Cys – Thr – Ser – Ile – Cys – Ser – Leu – Tyr – Gln – Leu – Glu – Asn – Tyr – Cys – Asn
His – Leu – Cys – Gly – Ser – His – Leu – Val – Glu – Ala – Leu – Tyr – Leu – Val – Cys
Gln
Asn
Val
Phe
Gly
Glu
Arg
Thr – Lys – Pro – Thr – Tyr – Phe – Phe – Gly


Remove the dog's pancreas
Islets of Langerhans isolated fom pancreas
Dog develops diabetes
Cells liquidised and solids filtered off
Solution injected back into dog
Dog's diabetes is treated successfully
Further experiments isolated and purified Insulin from the solution
© ABPI 2009

gene enzyme cuts out gene

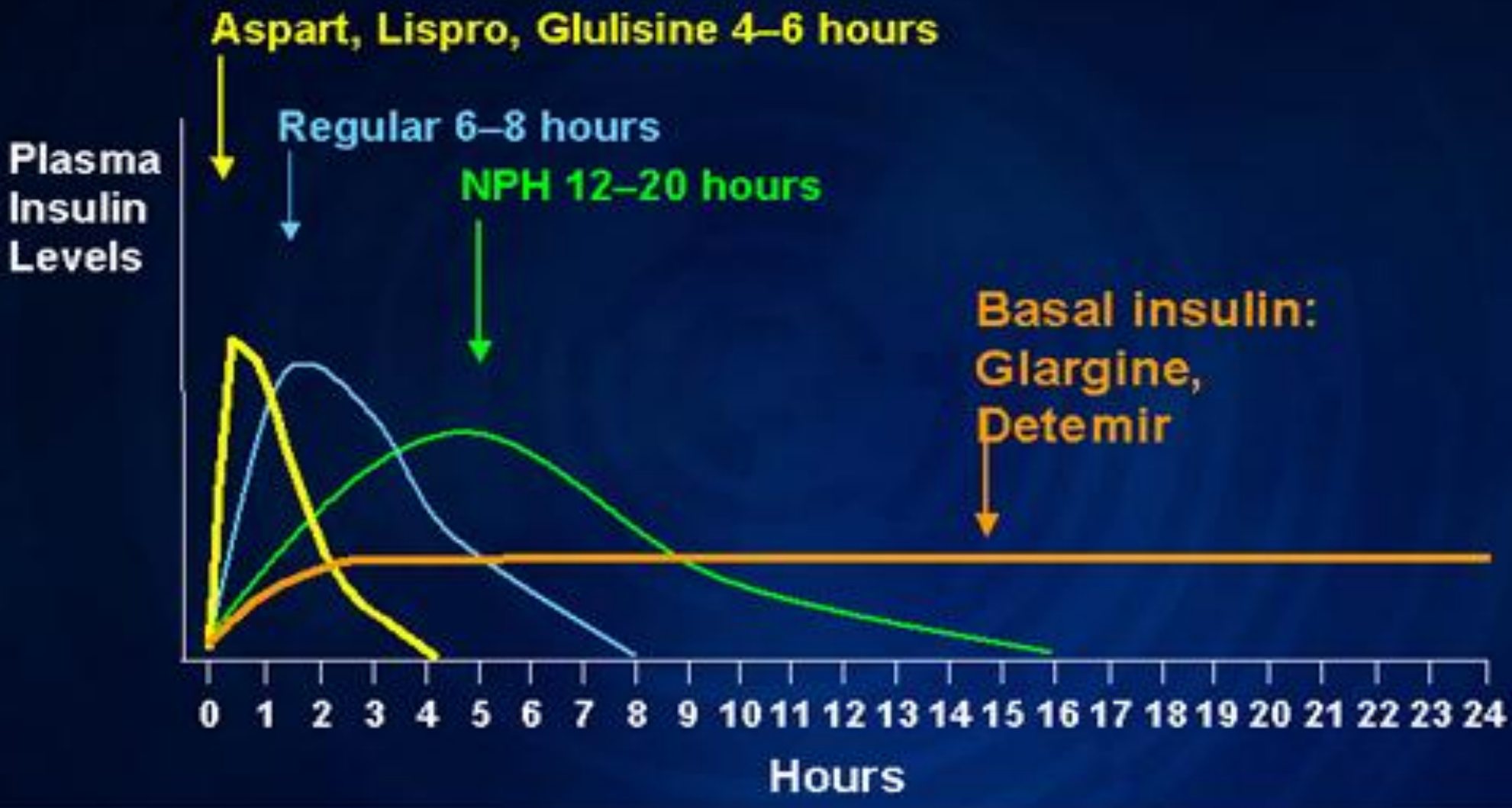
Enzyme cuts bacterial DNA and inserts insulin gene



8 Grow trillions of new insulin-producing bacteria.

Figure 4-3 (4) Biology Today, 3/e (© 2004 Garland Science)

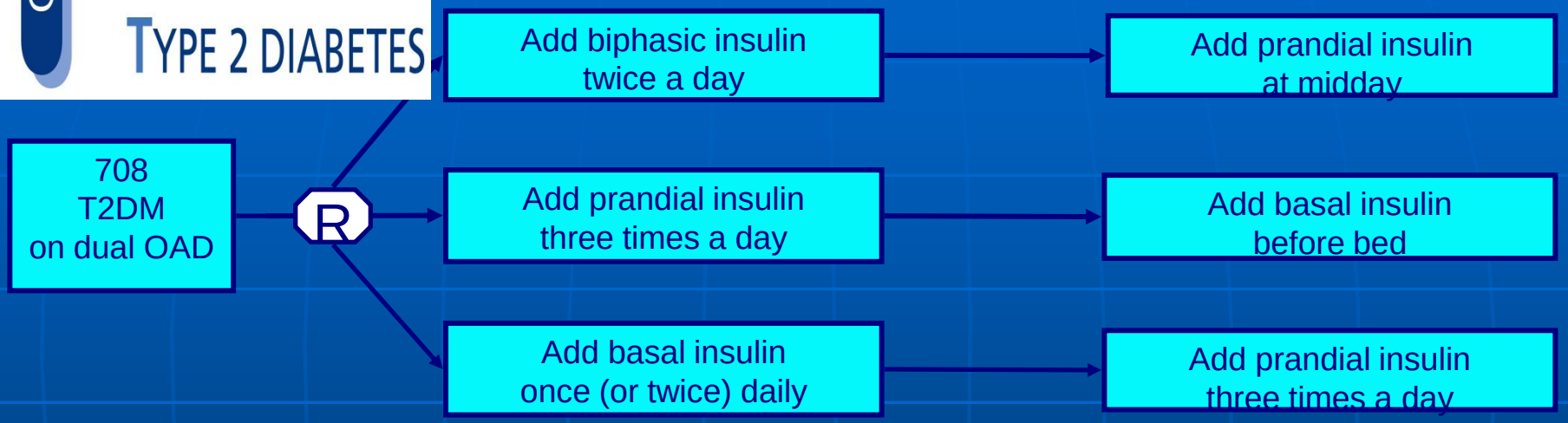
Action Profiles of Injectable Insulins



Type 2 Diabetes Insulin Options

- Basal
  - NPH/Protophane at bedtime and/or a.m.
  - Glargine once daily at any time of the day(*If unacceptable hypos after 3 months on NPH or Protophane)*
  - Detemir once or twice daily (*not funded*)
- Premixed
  - Premixed once or twice a day
- Pre Mixed Analogues :Humalog Mix 25 ,Humalog Mix 50/50
  - Meal-time insulin
  - Multiple daily injections (meal-time + basal)

TREATING TO TARGET IN TYPE 2 DIABETES



* *Intensify to a combination insulin regimen in year one if unacceptable hyperglycaemia*

Three-arm trial in 708 patients with type 2 diabetes from 58 UK and Irish centres
Evaluating addition of three different analogue insulin regimens to dual oral antidiabetic therapy
Open-label randomisation to:

- Twice a day biphasic insulin (NovoMix 30)
- Three times a day prandial insulin (NovoRapid)
- Once a day basal insulin (Levemir) before bed, with a morning injection added if necessary

N Engl J Med 2007; 357: 1716-30

Outcomes at One Year

Primary

- To compare HbA_{1c} levels achieved by the three regimens

Secondary outcomes include:

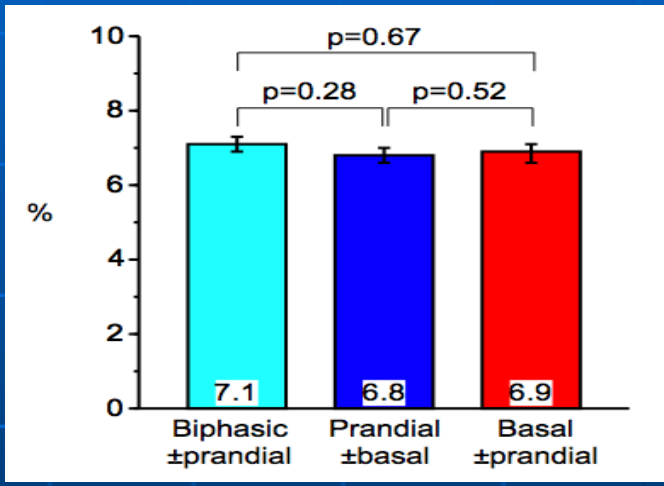
- Proportion with HbA_{1c} ≤6.5%
- Proportion with unacceptable hyperglycemia
  i.e. HbA_{1c} >10% or two successive values >8.5%
  at or after 24 weeks
- Hypoglycaemia rates
- Impact on body weight
- Quality of Life (EQ-5D)
- Eight-point self-measured capillary glucose profiles
- Proportion requiring a morning basal insulin injection

Results Comparisons

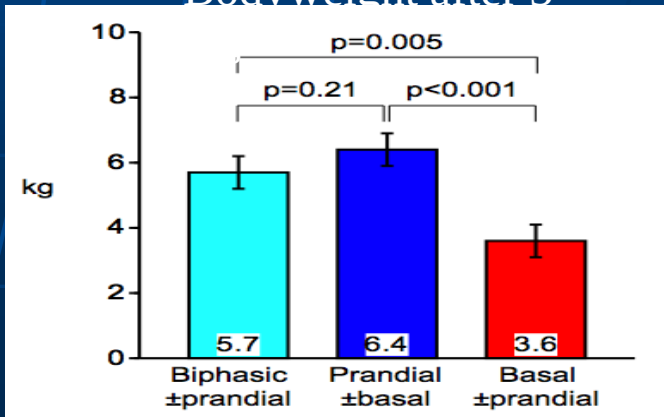
- **Results – Harms:**
- • Basal Insulin: *gained less weight than those in the biphasic or prandial insulin groups*
- Weight gain in Kg
- *Basal* *+1.9 kg*
- *Bi –Phasic* *+ 4.7 kg and*
- *Prandial* *+ 5.7 kg, P<0.001).*
- • *The weight gain was significantly higher in the prandial group than the biphasic group (P=0.005).*
- • Basal group: *significantly less likely to experience more severe hypoglycaemia than those in the biphasic or prandial groups (median: 0, 3.9 and 8.0 events per patient per year).*

- **Results – benefits:**
- • The reduction in HbA1c from baseline: -
-1.3% in the biphasic group,
-1.4% in the prandial group
- 0.8% in the basal group.

Hba1c after 3 yrs



Bodyweight after 3



Summary 4T Study after 3 yrs

- Three quarters of patients added a second insulin
- Those commencing therapy with a basal or prandial insulin more often achieved glycaemic targets than patients commencing with a biphasic insulin
- Patients commencing therapy with basal insulin had fewer hypoglycaemic episodes and less weight gain

These findings provide clear evidence in people with type 2 diabetes to support starting insulin therapy with a once a day basal insulin, and then adding a mealtime insulin if glycaemic targets are not met

Basal Insulin Summary

- One injection a day, with two capillary glucose tests for dose titration
- One third of patients require a morning insulin injection in addition
- More patients require a second insulin formulation than with Biphasic or Prandial insulin
- Basal slightly less HbA_{1c} lowering than with Biphasic or Prandial insulin
- Basal Insulin causes less weight gain and less hypoglycaemia than with Biphasic or Prandial insulin
- No change in QoL as assessed by EQ-5D

N Engl J Med 2007; 357: 1716-30

What about their oral Medications ??

- Hang on!!!!!!

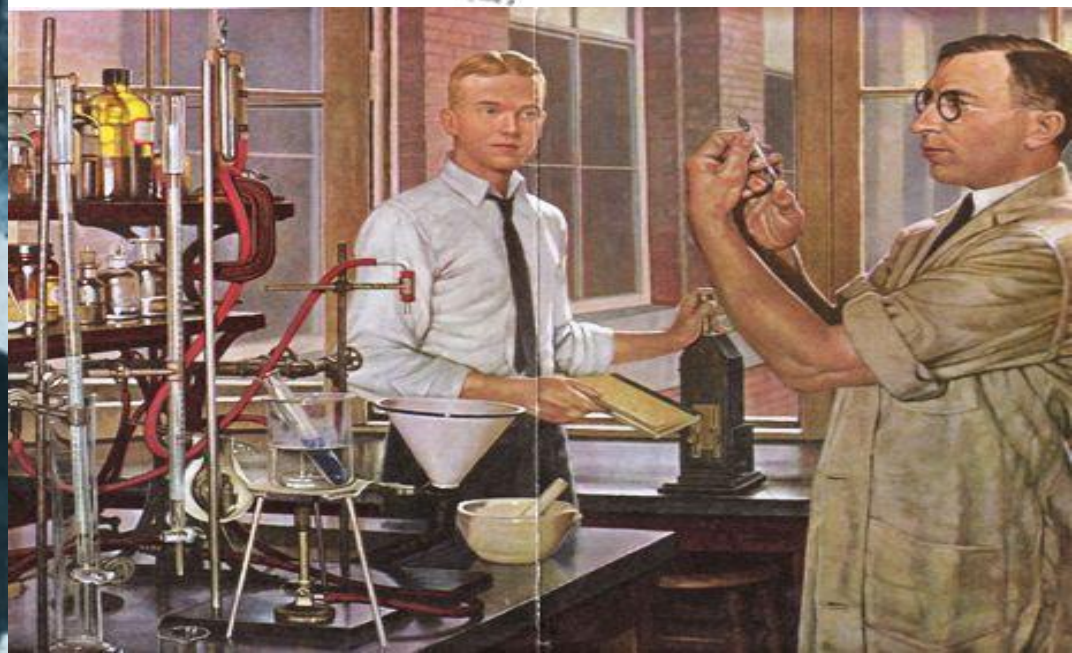
- Don’t throw away the Metformin????????

Metformin and Insulin: the benefits *Arch Intern Med. 2009;169(6):616-625*

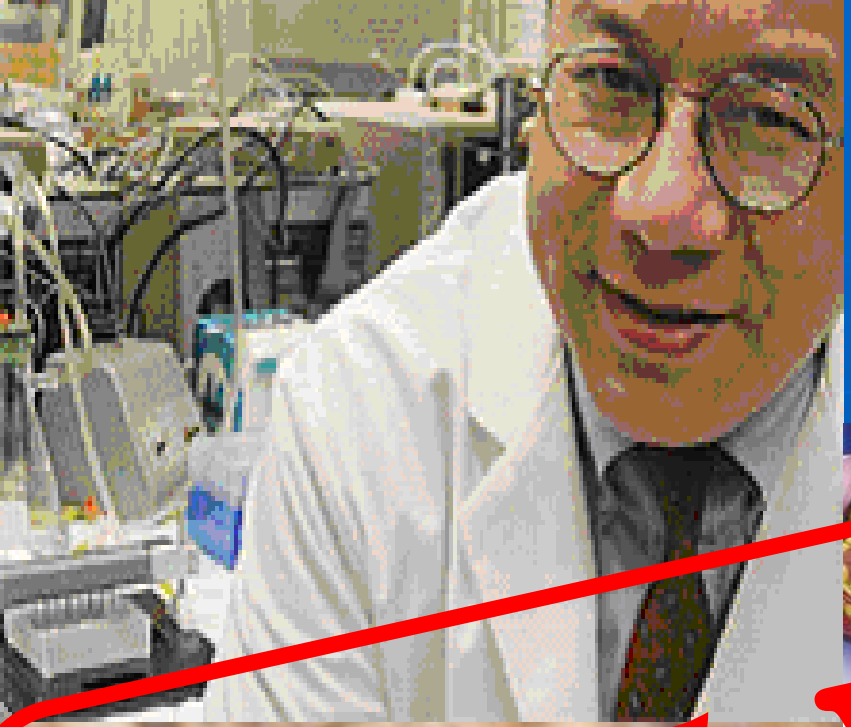
- 390 patients RCT with metformin 850 tds or placebo added to insulin with mean 4.3 year follow-up
- Metformin patients on average 0.4% better HBA1C, 3.07kg lighter
- Needed ~20 units less insulin
- Lower macrovascular event rate (NNT 16)

FOOD FOR THOUGHT!!!!!!!!

Soon after its discovery, insulin captivated media attention (Banting Digital Library)

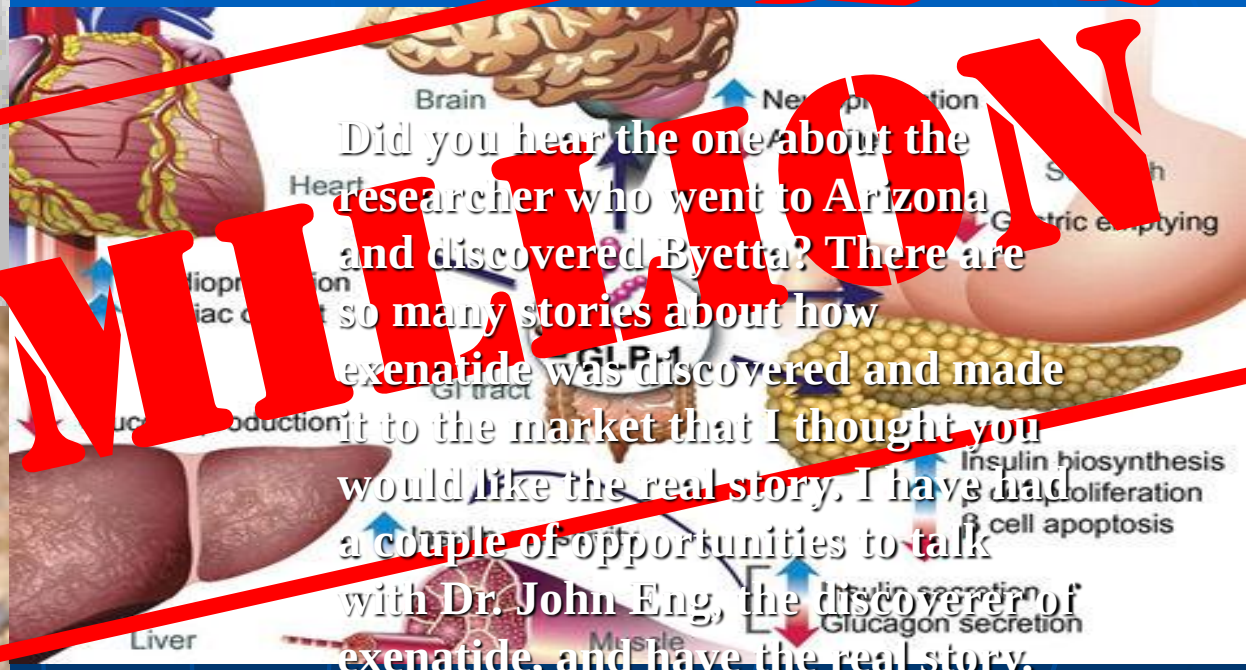


FOOD(*Money*) FOR THOUGHT!!!!!!!!



Thought for food!!!!!!!!

Dr. John Eng's Research Found That The Saliva Of The Gila Monster Contains A Hormone That Treats Diabetes Better Than Any Other Medicine



Did you hear the one about the researcher who went to Arizona and discovered Byetta? There are so many stories about how exenatide was discovered and made it to the market that I thought you would like the real story. I have had a couple of opportunities to talk with Dr. John Eng, the discoverer of exenatide, and have the real story.

$325 MILLION


THANK YOU!!!!

References

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