

Hypoglycaemic disorders

1. Hypoglycaemia in patients with diabetes mellitus
2. Hypoglycaemia in non-diabetic patients
3. Clinical, laboratory and imaging diagnosis
4. Case report
5. GLP-1 receptor scintigraphy
6. Summary

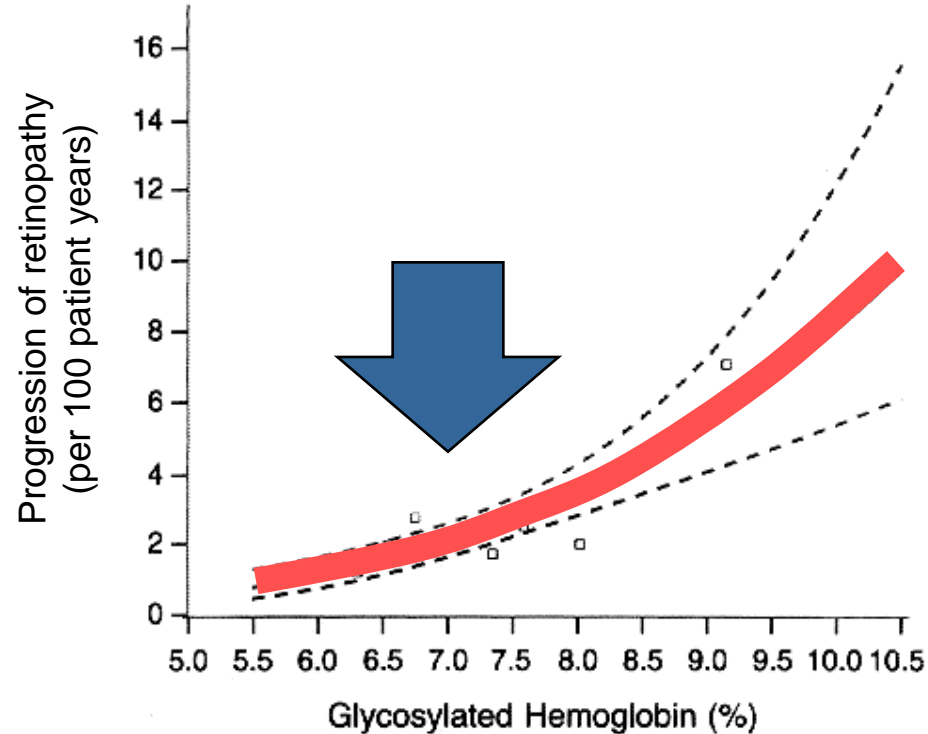
Christoph Henzen



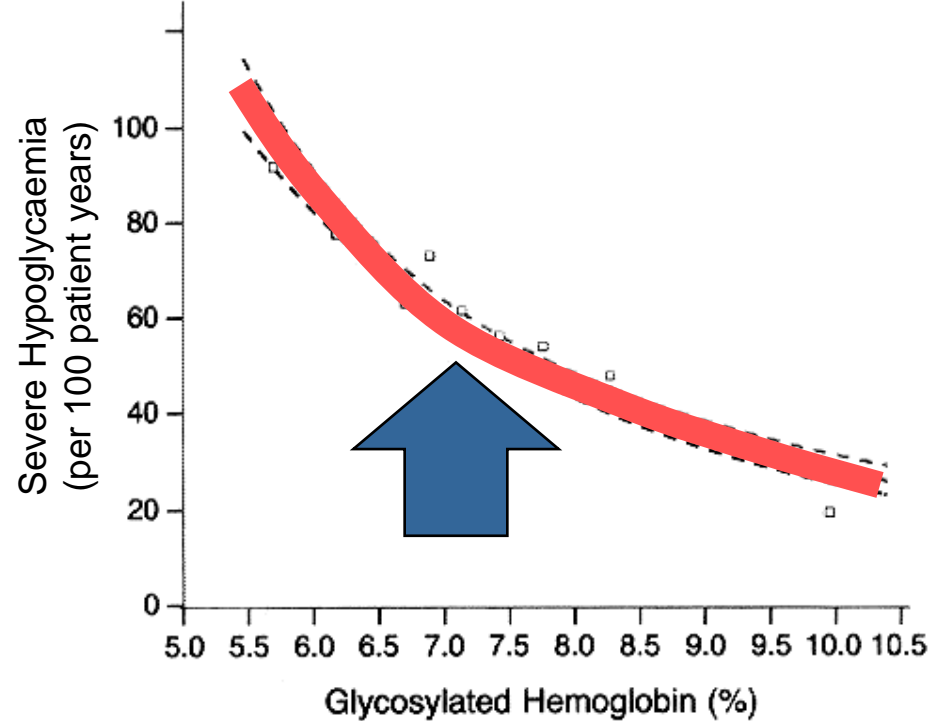
Hypoglycaemia in patients with diabetes mellitus

Goal of antidiabetic treatment

DCCT 1993

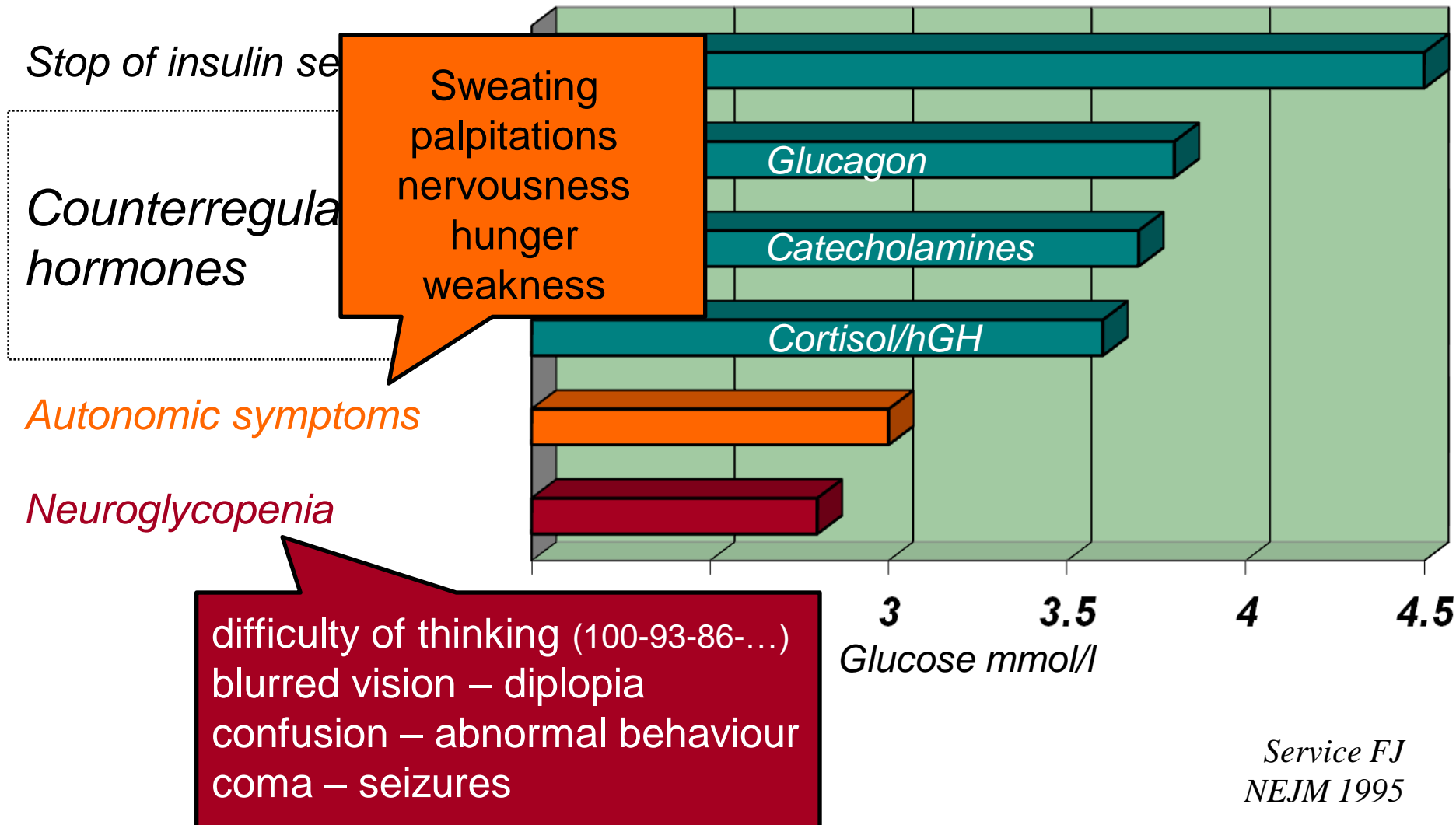


complications



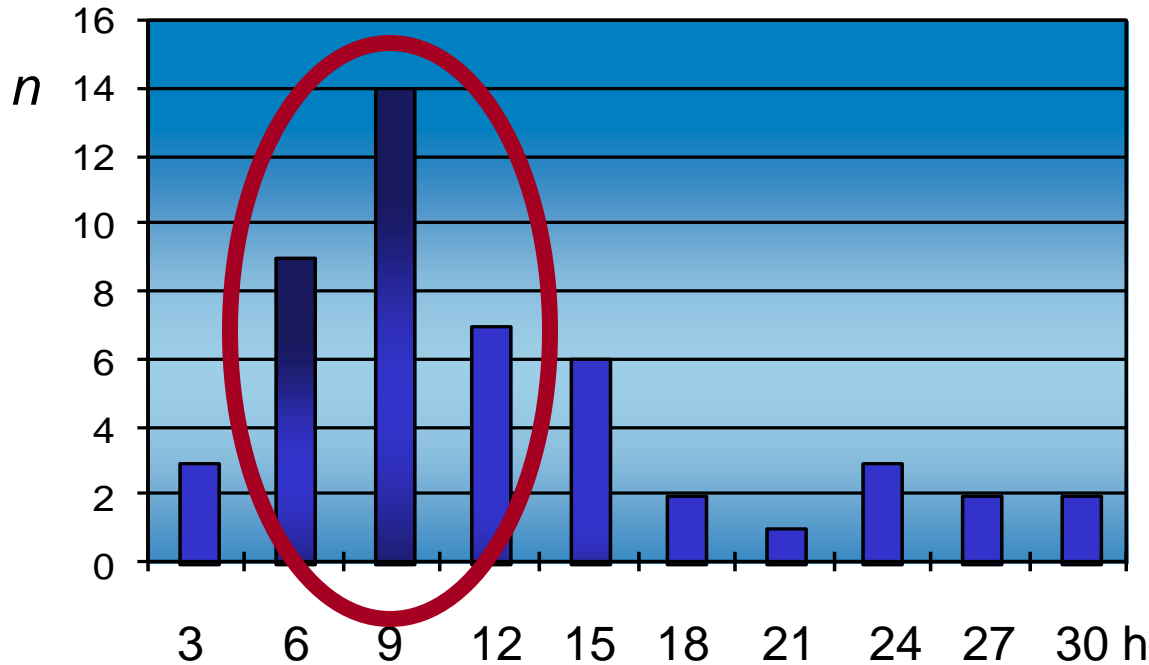
hypoglycaemia

Physiologic responses to hypoglycaemia



“Post-exercise late hypoglycemia”

MacDonald MJ, Diab Care 1987



Type 1 diabetes: n=300

Late hypoglycaemias
over 2 years

36 grade IV, 10 grade III

accumulation of hypos
6-15 h after physical
activity, 2.00-8.00 am

1. Reduce insulin dose: 5-10% of daily dose for 1h of activity
2. Extra carbohydrates: 10-40g / h of physical activity

Alcohol and hypoglycaemia

Alcohol

Gluconeogenesis

Plasma-Insulin +

Lactate-Glucose

Recycling -

Sulfonylureas +

Glucagon deficiency +

Oxidation FFA -

Hypo

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1548 ICU patients (13% with diabetes mellitus)

Mean blood glucose: 5.7 vs. 8.5 mmol/l

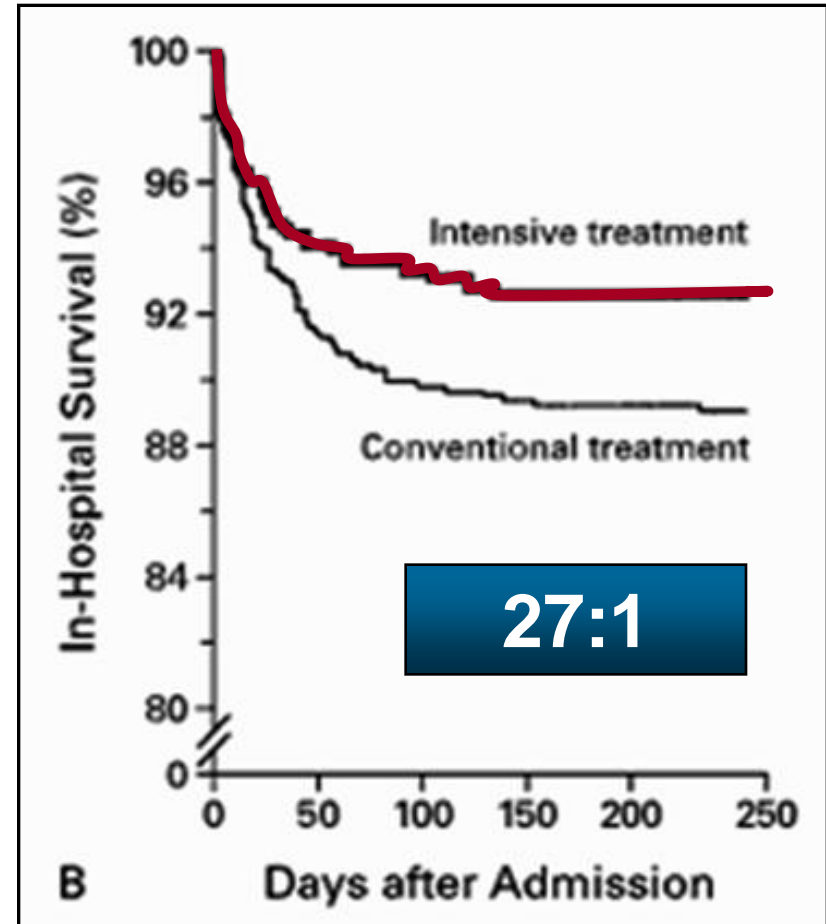
Mortality 4.6% vs. 8.0% = reduction of 34%

Reduction of bacteremia 46%

Acute kidney failure 41%

Ec-transfusions 50%

Critical Care Illness 44%



Glucose in the ICU?

Trial Name (Source) [†]	No. of Patients	Type of ICU	Primary Outcome	Rate of Outcome		Odds Ratio (95% CI)
				Intensive Glucose Control	Conventional Glucose Control	
				<i>percent</i>		
Leuven 1 (Van den Berghe et al. ³)	1548	Surgical	Death in ICU	4.6	8.0	0.58 (0.38–0.78)
Leuven 2 (Van den Berghe et al. ⁴)	1200	Medical	Death in hospital	37.3	40.0	0.94 (0.84–1.06)
Glucontrol (Devos et al., ⁵ Preiser J.C.: personal communication)	1101	General	Death in ICU	16.7	15.2	1.10 (0.84–1.44)
WISEP (Brunkhorst et al. ⁶) [§]	537	General	Death at 28 days	24.7	26.0	Not reported
NICE-SUGAR ⁷	6104	General	Death at 90 days	27.5	24.9	1.14 (1.02–1.28)
SPECS (Agus et al.)	980	Surgical	<i>Infection/1000d</i>	8.6	9.9	0.67 (0.4-1.59)
			<i>30-d mortality n</i>	5	6	
			<i>In-hospital</i>	11	11	
			<i>Length in ICU...</i>			

Is the door closed on studying glucose homeostasis in the critically ill? No, but it should be closed on the routine normalization of plasma glucose in critically ill adults and children.

*Inzucchi SE, Siegel ME. NEJM 2009;360:1346-
Agus MS et al. NEJM 2012;367:1208-
Kavanagh BP. NEJM 2012;367:1259-*

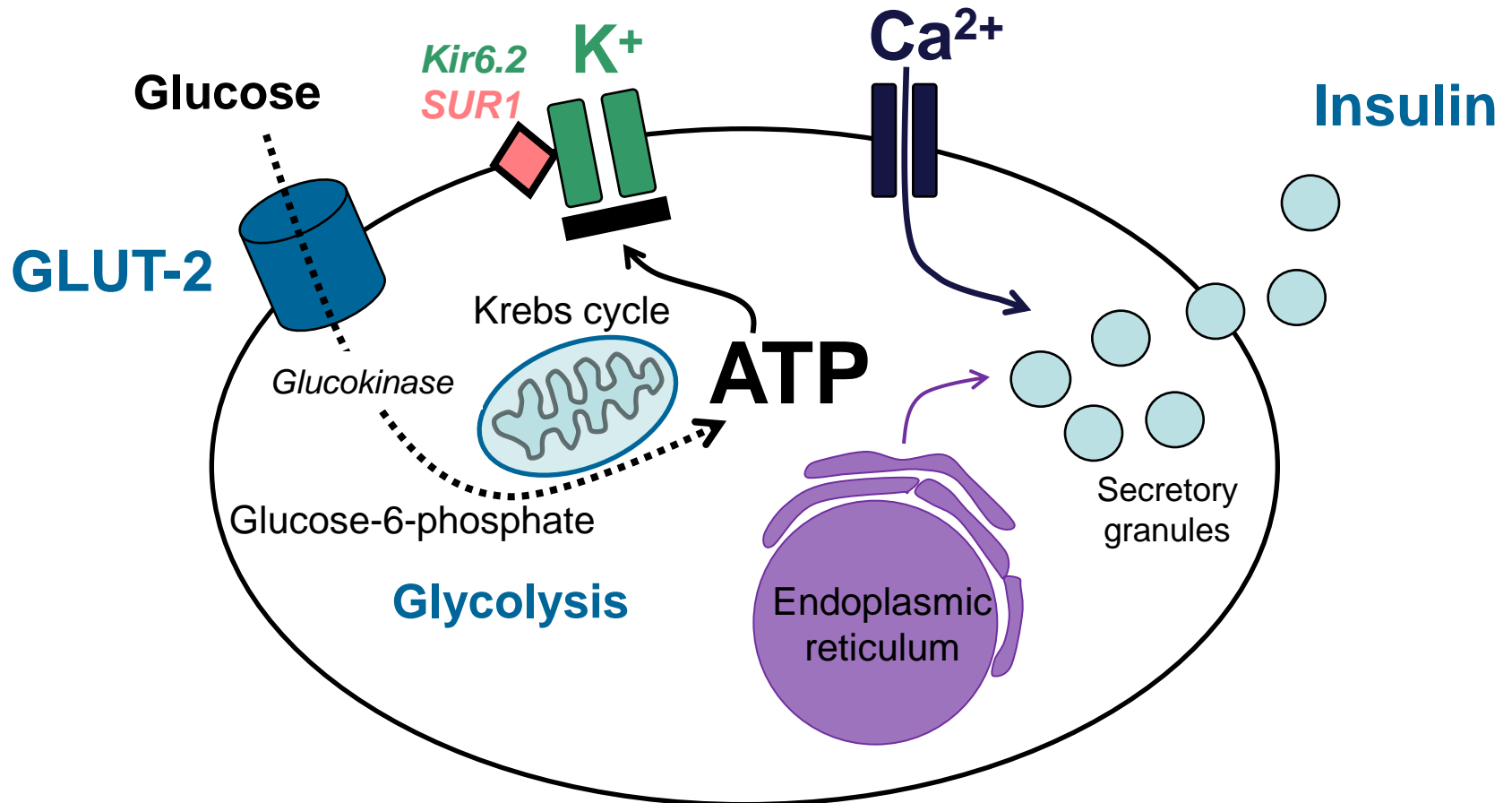
Hypoglycaemia in patients with diabetes mellitus

1. Counterregulation to hypoglycaemia is impaired in diabetic patients.
2. Symptoms of hypoglycaemia differ for different persons but are consistent in one person.
3. Physical activity and alcohol are the most common causes → insulin adjustment!
4. Near-normoglycaemia in critically ill patients?

1. Counterregulation to hypoglycaemia is impaired in diabetic patients.
2. Symptoms of hypoglycaemia differ for different persons but are consistent in one person.
3. Physical activity and alcohol are the most common causes → insulin adjustment!
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Hypoglycaemia in patients without diabetes mellitus

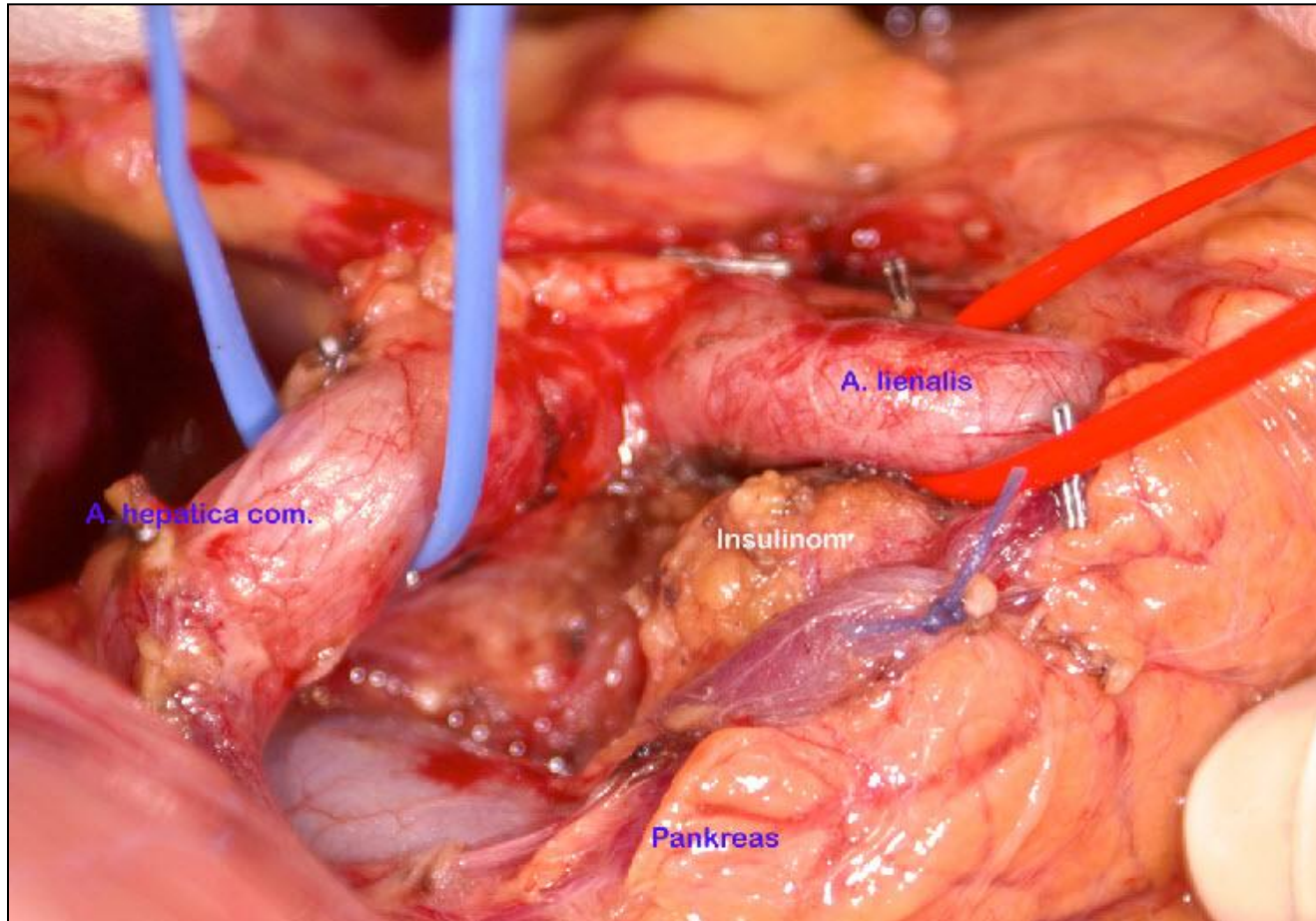
Pancreatic beta cell: coupling of glucose sensing and insulin secretion





Confirmed hypoglycaemia <2.5 mmol/l
Neuroglycopenic symptoms
Relief after glucose ingestion

Allen O. Whipple 1881-1963



Clinical classification of hypoglycaemia

Healthy-appearing?

Drugs

Sulfonylurea
Betablockers
Salicylates
Quinine
Haloperidol
Alcohol

Insulinoma

Factitious Hypoglycaemia

Extreme exercise

Ketotic Hypoglycaemia

Autoimmune insulin syndrome

Ackee fruit intoxication

Ill-appearing?

Sepsis

heart-/kidney failure

anorexia

lactic acidosis

Addison's disease

hypopituitarism

pheochromocytoma operation

glycogen storage diseases

hereditary fructose intolerance

galactosemia

Carnitine deficiency

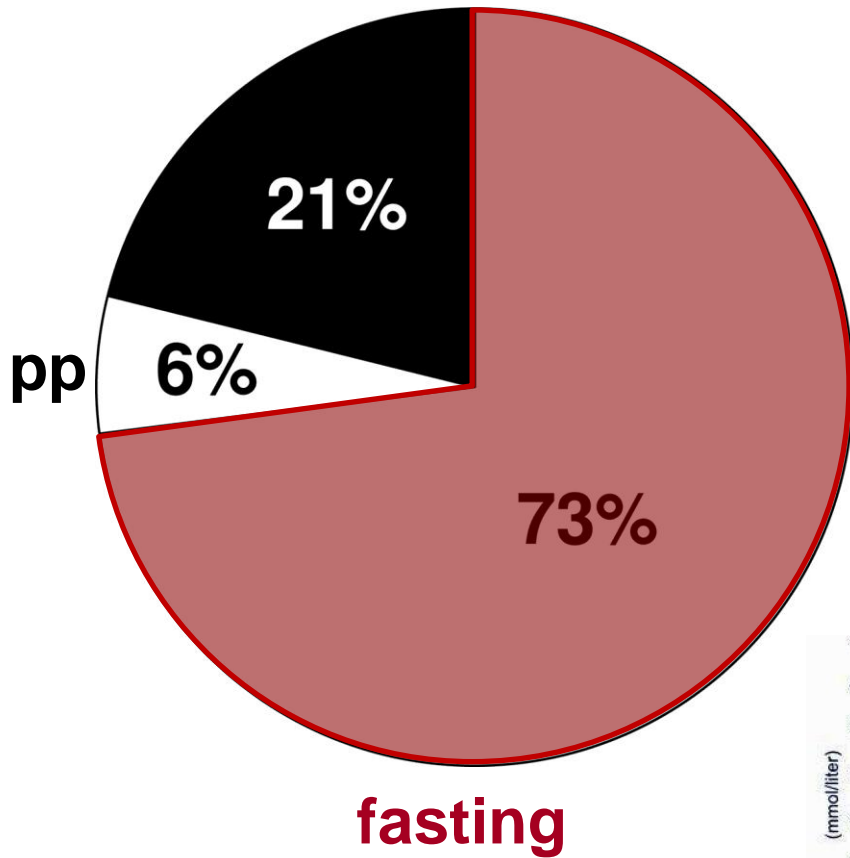
Wiedemann-Beckwith syndrome

Reye's syndrome...

drugs...

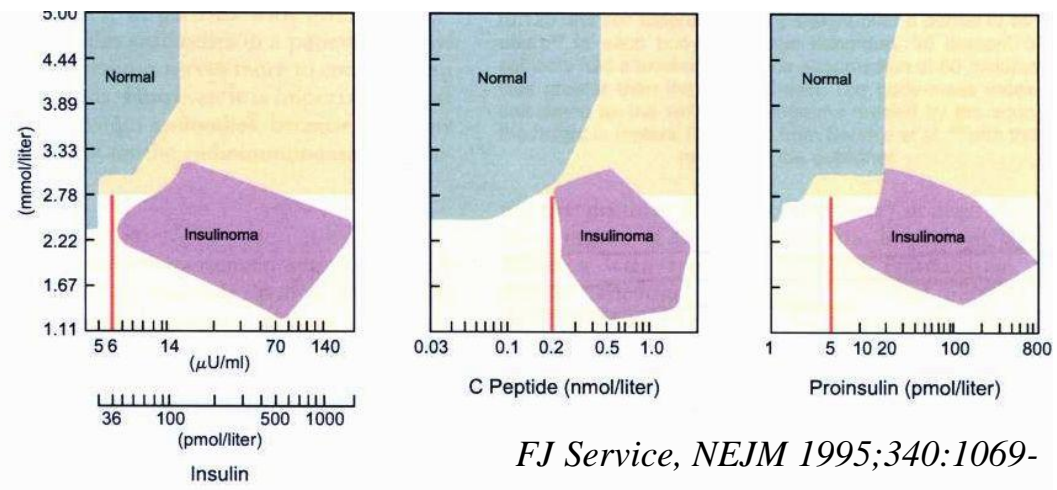
Hypoglycaemia after gastric-bypass-surgery

Hypoglycaemia in patients with insulinoma (n=214)



Diagnosis: Laboratory findings

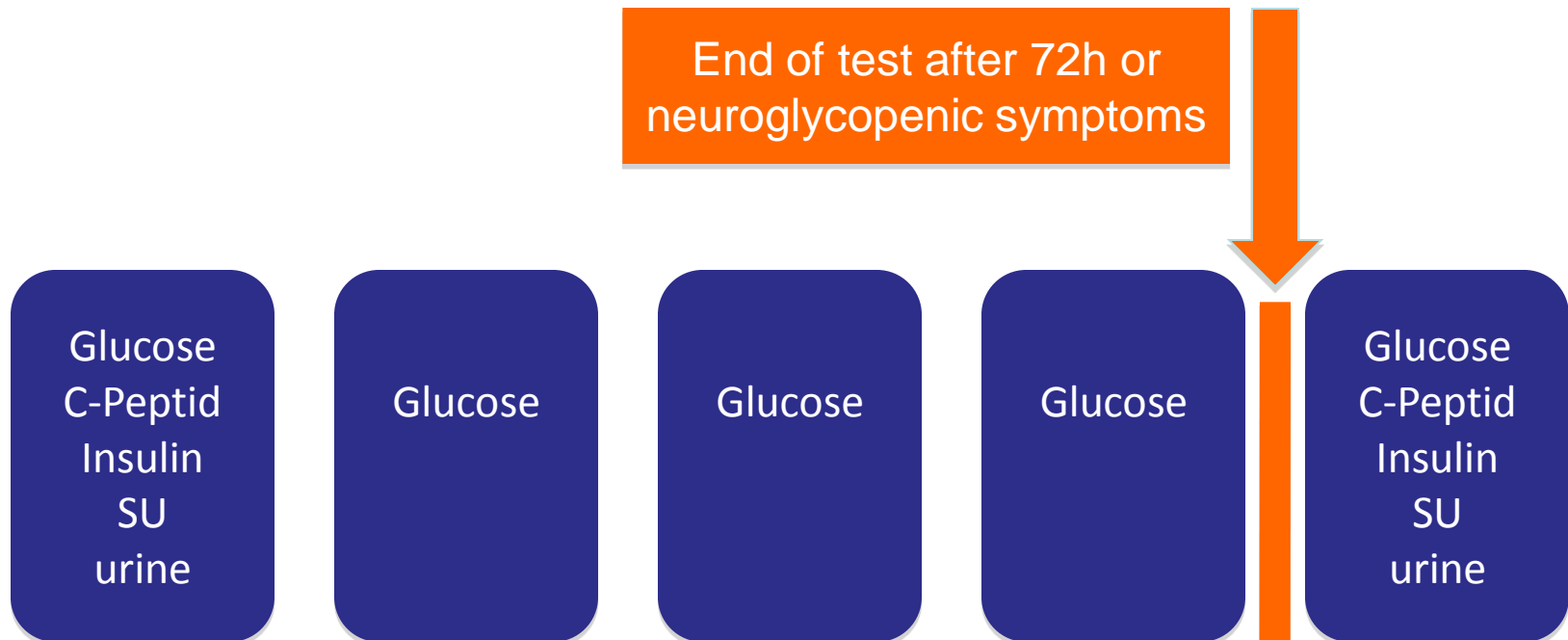
	Sensitivity	Specificity
Insulin	93%	95%
C-peptide	100%	60%
Proinsulin	100%	68%
BHOB	100%	100%



72-hour fast

Before testing:

- Exclusion of adrenal insufficiency
- Measurement of insulin antibodies
- 8 hour fast



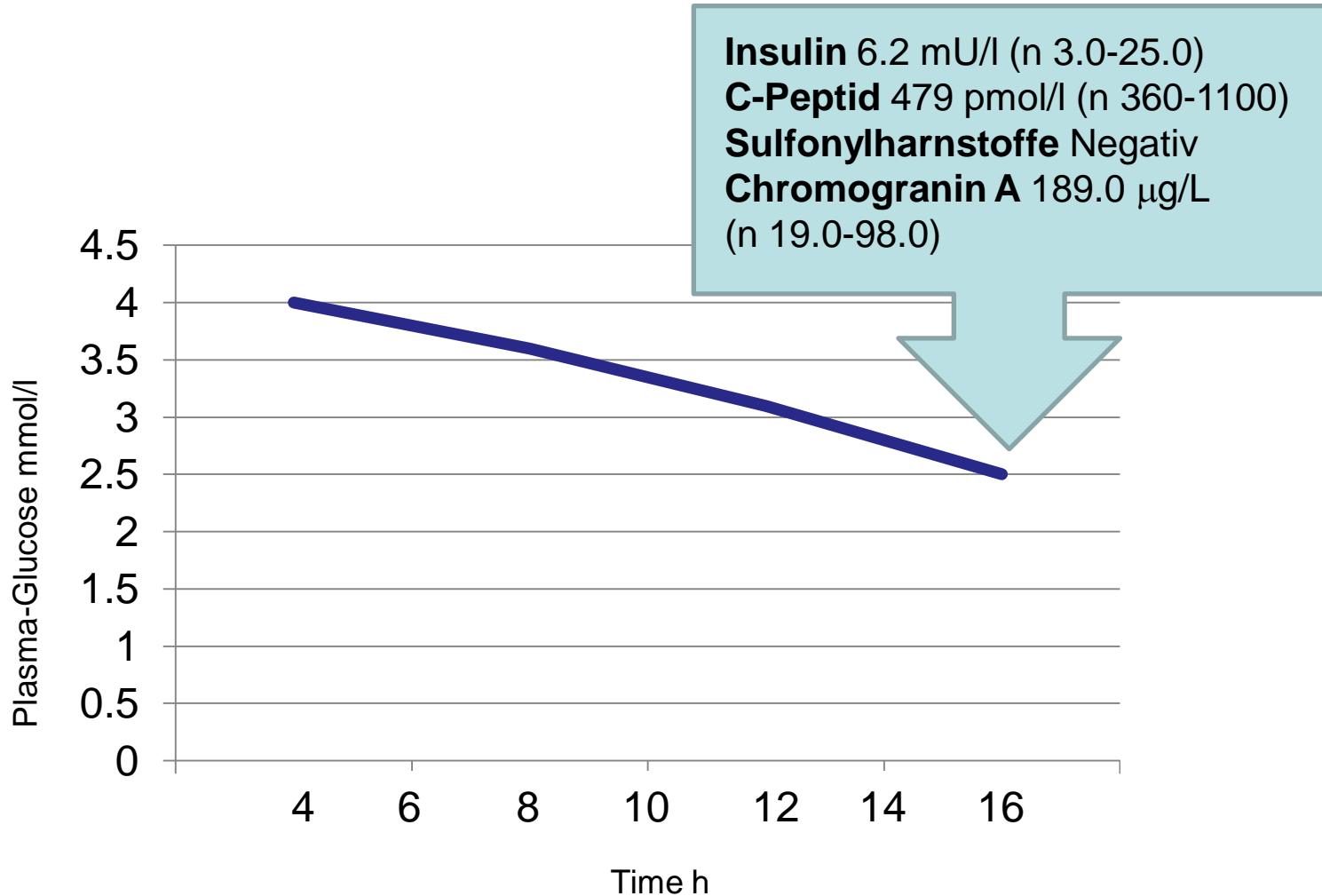
Case report

A 73-year old lady complains about sweating, restlessness, dizziness, occurring over the last 10 months, predominantly before meals and during the night.

Because her husband suffers from insulin-dependent diabetes she is familiar with these symptoms, and she repeatedly measures her blood sugar as low as 2.1 mmol/l.

After ingestion of dextrose there is immediate relief of the symptoms, and the lady finds out that regular meals every 4 hours prevent the symptoms.

72-hour fast



Diagnostic evaluation of suspected hyperinsulinism (n=5) (1)

Parameter	Pat. A	Pat. B	Pat. C	Pat. D	Pat. E
Age	65	53	79	62	31
Gender	m	w	w	m	m
Sy / Dx (months)	6	12	10	12	2
Symptoms	Leg palsy Dysarthria	Confusion	Confusion Palpitations	Confusion Hemiparesis „burn-out“	Confusions Syncope
Fasting	X	X	X	X	X
Postprandial	–	X	–	–	X
Weight	+ 3 kg	+ 6 kg	stable	stable	+ 7 kg

72-h fast (results) (2)

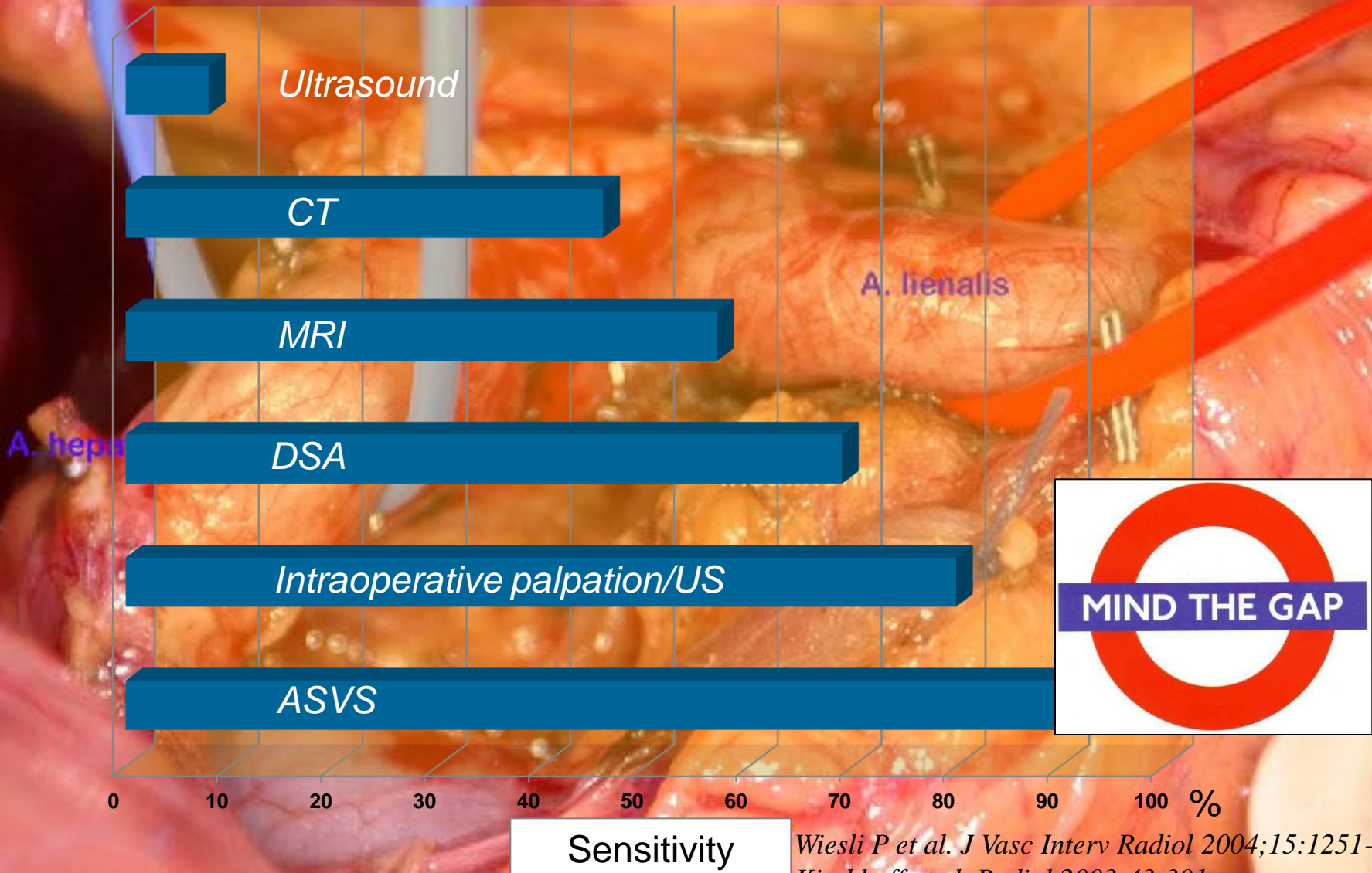
Parameter	Pat. A	Pat. B	Pat. C	Pat. D	Pat. E
Glucose Start (mmol/l)	3.4	3.1	3.6	3.3	4.6
Glucose Stop (mmol/l)	1.7	1.9	2.4	1.8	1.8
End of Test after (h)	44	17	16	30	47
Insulin (pmol/l)	56.2	13.8	37	65.4	12
C-Peptide (pmol/l)	1120	350	479	672	447
Ketones	+	negative	++	++	+

Sulfonylurea: all negativ at beginnning and end of 72-h fast

Localization procedures (3)

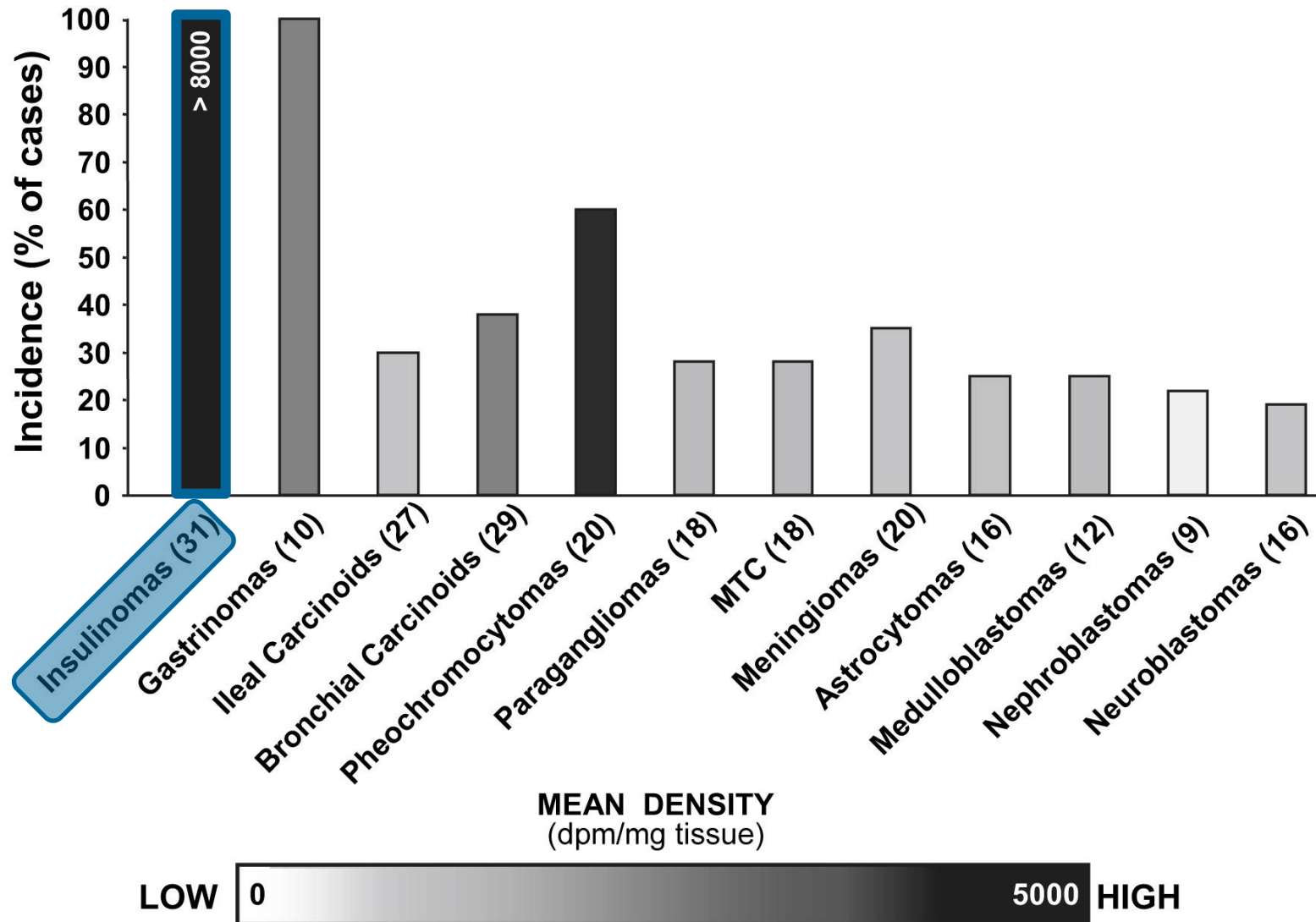
Parameter	Pat. A	Pat. B	Pat. C	Pat. D	Pat. E
MRI / CT	Pos.	Neg.	Neg.	Neg.	Neg.
GLP1 Szintigr.	Pos.	Pos.	Pos.	Pos.	Neg.
Additional imaging	–	–	–	–	EUS art. Calcium-Stimulation
Palpation OP	Pos.	Pos.	Pos.	Neg.	N.A.
Localization	head	corpus	corpus	corpus	N.A.
Therapy	enucleation	resektion L	enucleation	resektion L	Diazoxid
Histology size	15 mm	9 mm	7 mm	12 mm	N.A.
MIB-1	5%	<1%	<5%		
recurrence	–	–	–	–	–

Imaging procedures

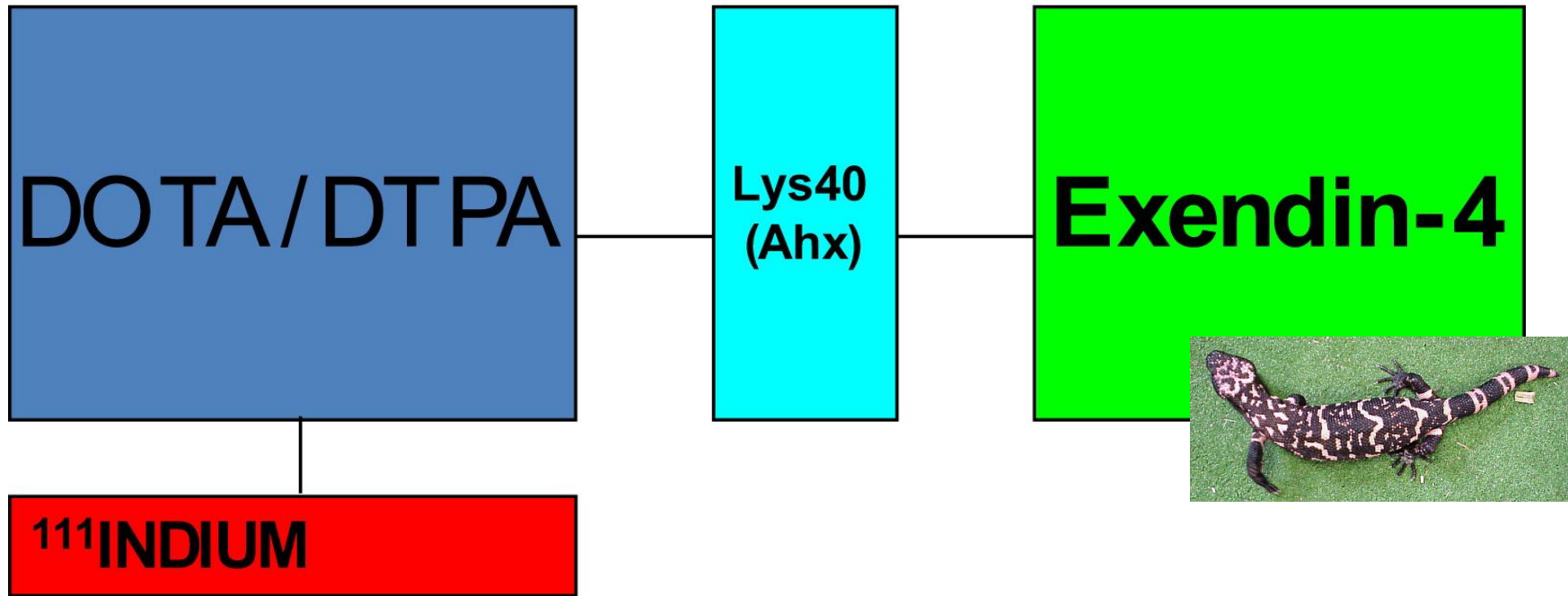


Wiesli P et al. *J Vasc Interv Radiol* 2004;15:1251-
Kirchhoff et al. *Radiol* 2003;43:301-
Druce M R et al. *EJE* 2010;162:971-978

GLP-1 receptors



Radioactive peptide → GLP-1 R



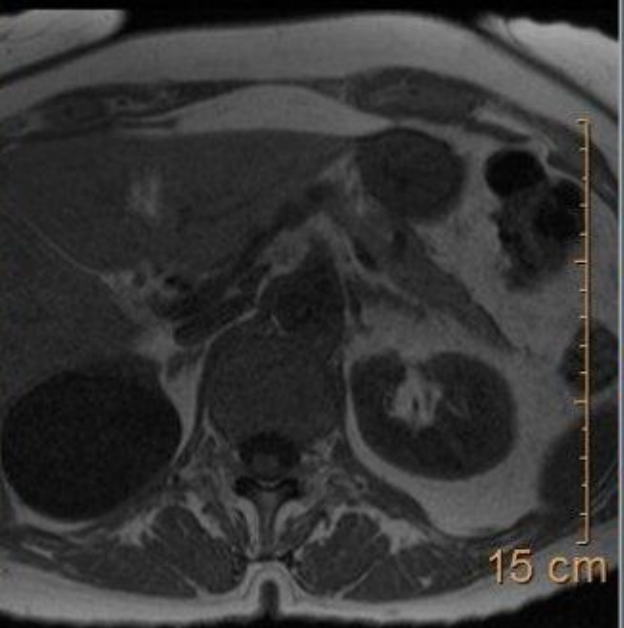
[Lys40(Ahx-DOTA/DTPA-¹¹¹In)NH₂]exendin-4

Glucagonlike Peptide-1 Receptor: An Example of Translational Research in Insulinomas: A Review

Christ E, Wild D, Reubi JC. Endocrinol Metab N Am 2010;39:791-800

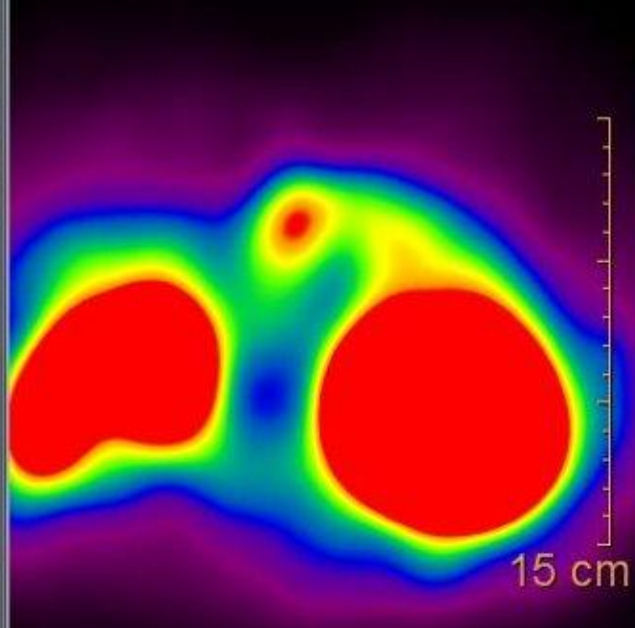
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M ND NORM / t1_tra_mbh_4mm pankreas
1/31/2012



312-1:4

RECONTOMO/TRANS-AC_24h_pi
12/5/2011

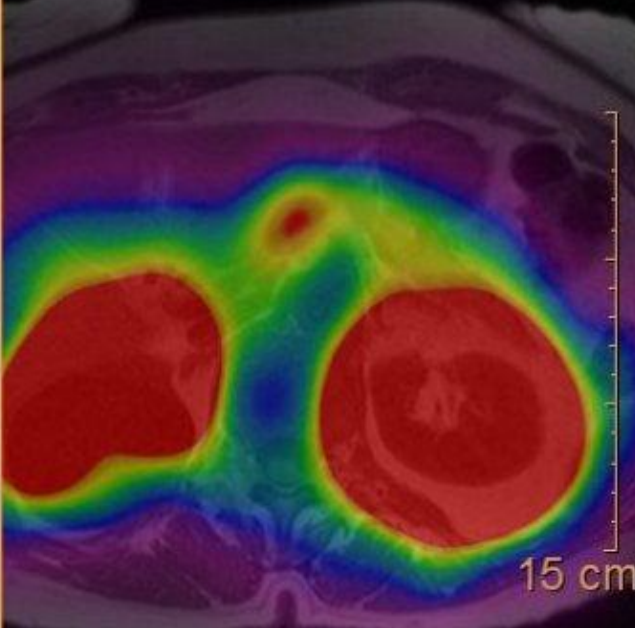


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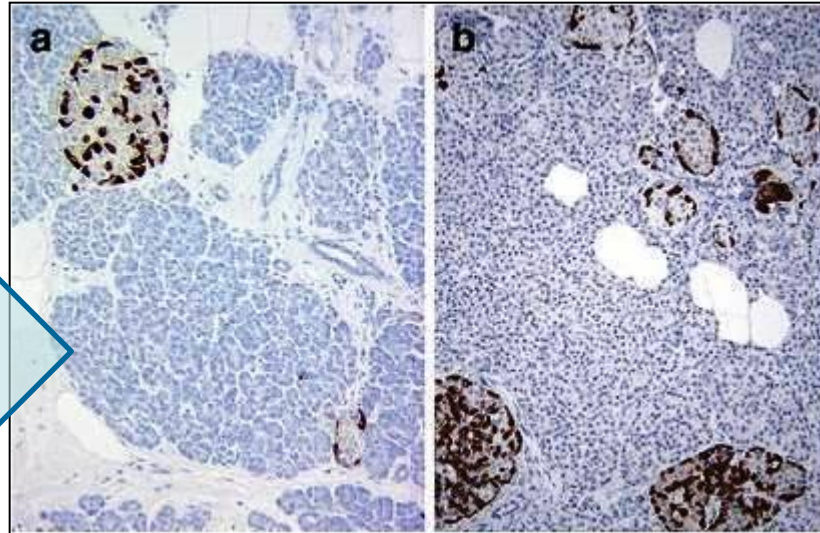
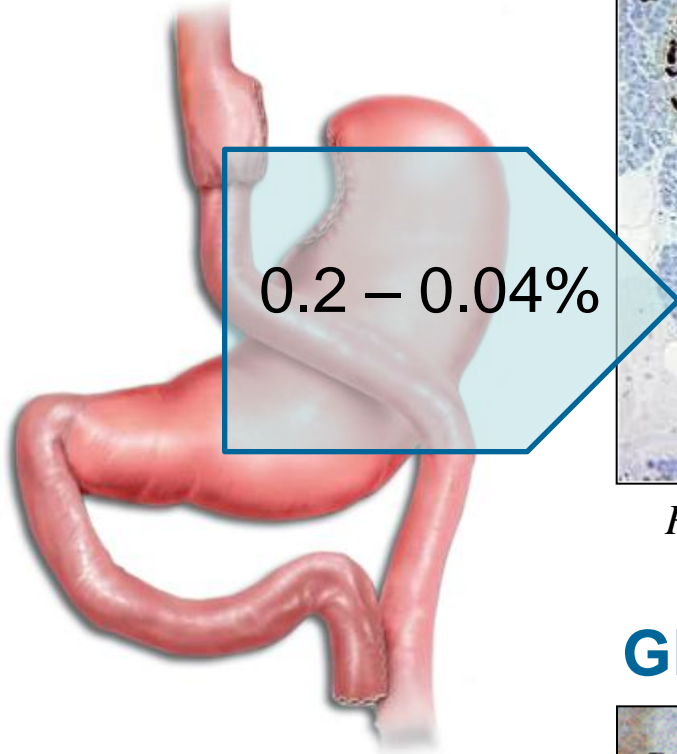
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NM: 12/5/2011
MR: 1/31/2012

03.02.2012 10:08

Serie 31293

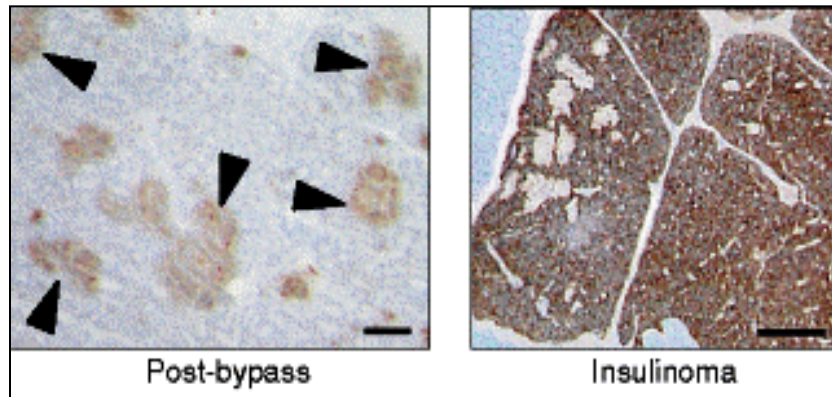


Gastric bypass operation and nesidioblastosis?



Patti ME et al. Diabetologia 2005;48:2236-

GLP-1 receptors?



*Reubi JC, Perren A, Christ E et al.
Diabetologia 2010;53:2641-*

Whipple-Trias

Patient's history

Symptoms (autonomic / neuroglycopenic)
fasting / postprandial
drugs / alcohol

Laboratory investigations

renal / liver function
adrenal insufficiency
Insulin antibodies

72-h fast

endogenous hyperinsulinism

Localization procedures

CT / MRI
EUS
GLP-1-receptor scintigraphy
arterial calcium-stimulation (ASVS)

Surgical exploration

intraoperative palpation
intraoperative US
Gamma probe

	<i>insulin</i>	<i>C-peptide</i>
insulinoma	+	+
SU (factitious)	+	+
insulin (factitious)	+	0
alcohol	0	0

Investigation in acute stage

Insulin, C-Peptide
Sulfonylurea
BOHB, Proinsulin

Mixed meal test

Pharmacological therapy

Diazoxide
Octreotid
Everolimus

Surgical treatment

enucleation
Segment resection / distal resection
Whipple operation

Summary

1. Insulinoma are a rare disease (incidence 4/1Mio.)
2. Hypoglycaemia AND neuroglycopenic symptoms
3. Localisation-gap: GLP-1 receptor scintigraphy
4. CAVE: Malignant insulinoma (sst2 Rezeptoren)
5. Nesidioblastosis in adults (post gastric bypass vs. noninsulinoma pancreatogenous hypoglycemia)