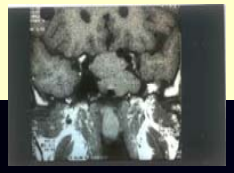
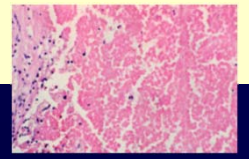

RICHARD
BURTON
CLINT
EASTWOOD
MARY
URE
WHERE EAGLES DARE

……An Impregnable Alpine fortress where only an Eagle may dare to enter

Secondary Diabetes -Where Eagles Dare

Nihal Thomas
MD DNB(Endo),MNAMS,FRACP (Endo) FRCP (Edin)
Professor,
Department of Endocrinology,
Diabetes and Metabolism
Christian Medical College,
Vellore,India





1.What is the relative contribution of

Fasting hyperglycaemia and postprandial hyperglycaemia to mean glycaemic values?

Glycaemic Control
-relative contributions

The contribution of Post prandial hyperglycaemia to Hba1C is upto 70% in well controlled individuals

The contribution of fasting hyperglycaemia to HbA1C is up 30% in those with poorly controlled diabetes mellitus
-Diabetes Care 2003, Monnier L.

2.How common is unrecognized hypoglycaemia in the well controlled patient with diabetes mellitus?

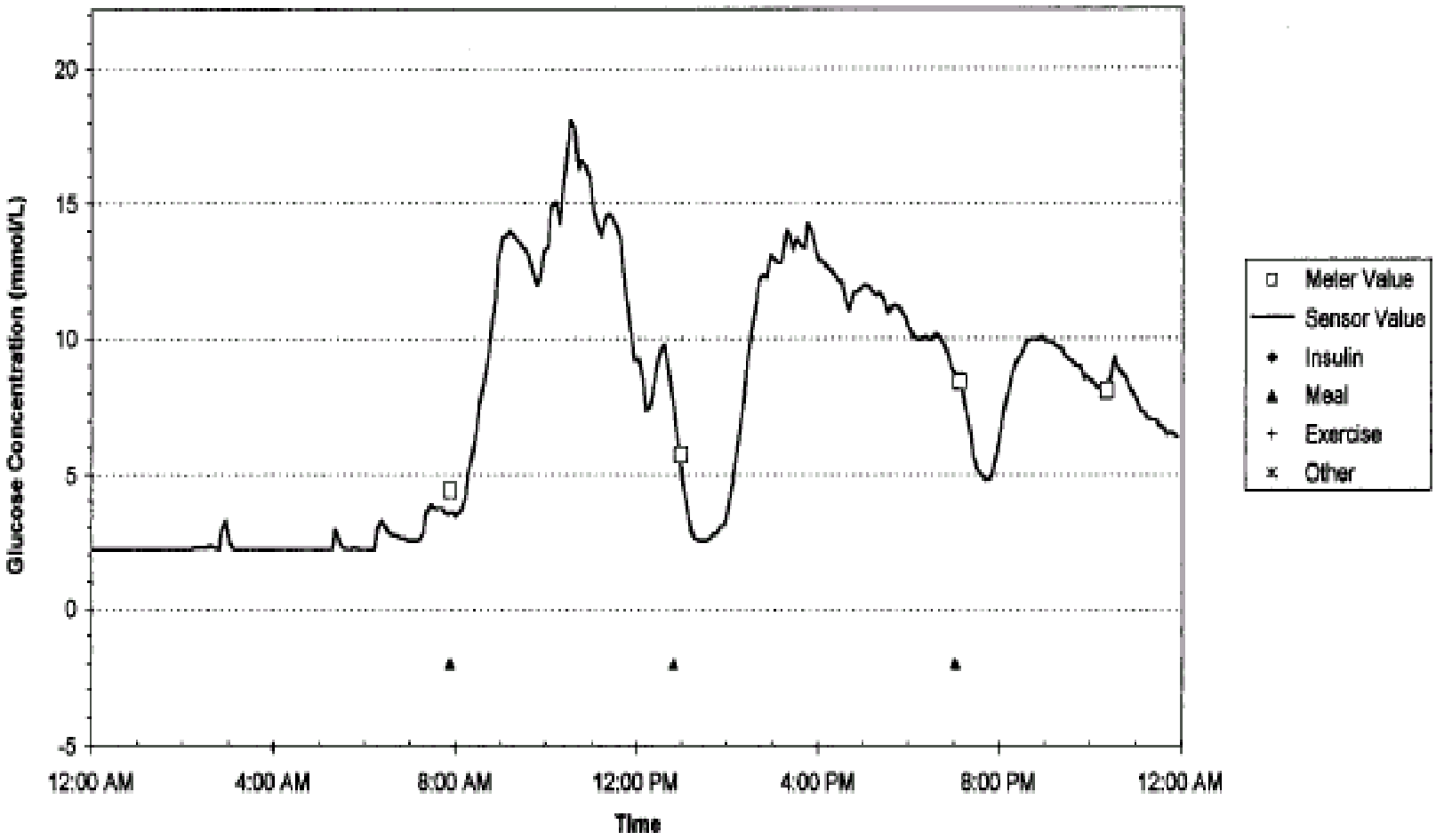
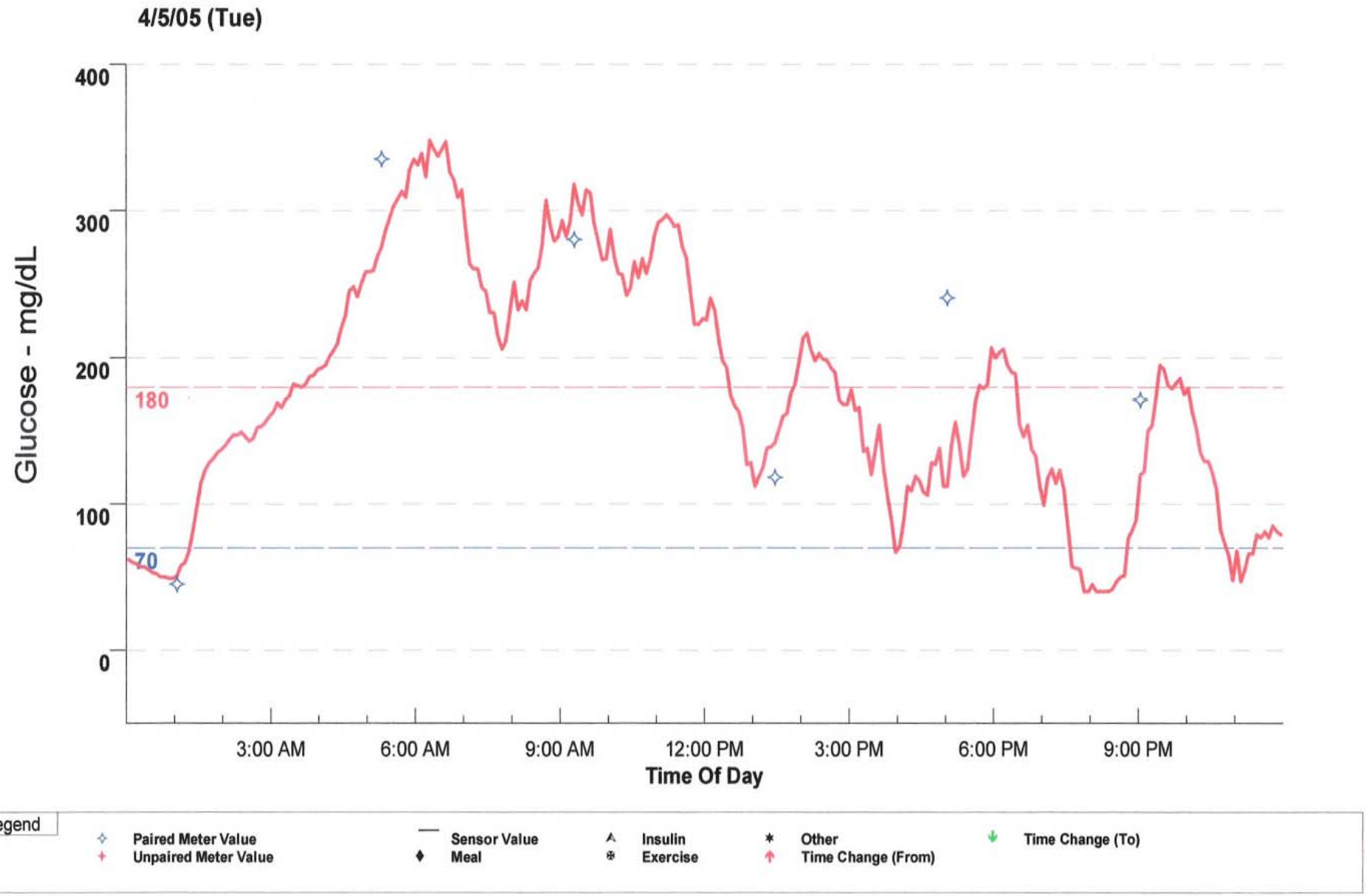


FIG. 1. Twenty-four-hour glucose profile demonstrating nocturnal hypoglycemia and significant daily postprandial glucose rises.

Sensor Daily Details

MiniMed Solutions: CGMS Sensor
MMT-7310 3.0B



Hypoglycaemia is present in upto 7% of the time in a day in individuals with well controlled diabetes mellitus

Diabetes Technology and Therapeutics
Hay LG, Wilmhurst EG.

However, Secondary Diabetes ...seems to be a different ball game

- **What is Secondary Diabetes?**

A Disorder of Diabetes……..
other than Type 1 or Type 2 Diabetes
- and an Alteration in Counter-regulatory hormone Homeostasis

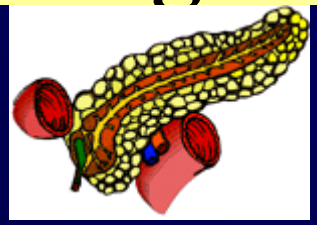
Classification

- Genetic defects of Beta cell function by mutation.
- Genetic defects in Insulin action.
- Exocrine pancreatic diseases.
- Endocrinopathies due to over production of counter regulatory hormones.
- Drugs or chemicals induced.
- Infectious diseases.
- Uncommon form of immune mediated diabetes.
- Other genetic syndrome with diabetes.

Classification

- Genetic defects of Beta cell function by mutation.
- Genetic defects in Insulin action.
- Exocrine pancreatic diseases.
- **Endocrinopathies due to over production of counter regulatory hormones.**
- Drugs or chemicals induced.
- Infectious diseases.
- Uncommon form of immune mediated diabetes.
- Other genetic syndrome with diabetes.

Regulatory Hormones a Background



Hypoglycaemic

Insulin

Glucagon-Like Peptide-1

Somatostatin

Proglycaemic

Glucagon

Catecholamines

Growth Hormone

Glucocorticoids

Somatostatin

Regulatory Hormones a Background

Hypoglycaemic

Insulin

Glucagon-Like Peptide-1

Somatostatin

Proglycaemic

Glucagon

Catecholamines

Growth Hormone

Glucocorticoids

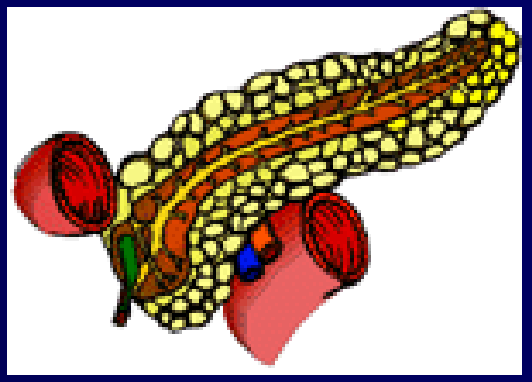
Somatostatin

Insulin : - ve

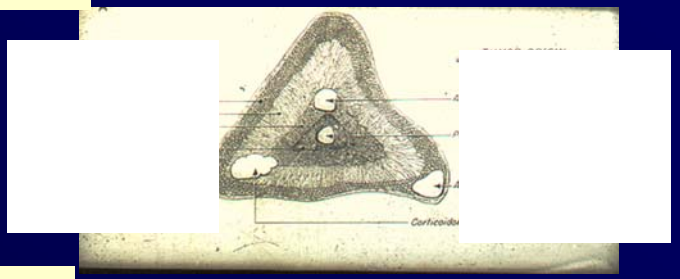
Glucagon: + ve

GLP-1: -ve

Somatostatin: +ve & -ve



Cortisol +ve



Catecholamines +ve

Liver

Growth

Hormone +v

Pituitary

Proglycaemic hormones…

Glucagon……..Ketogenic

Catecholamines…Ketogenic…

Glucocorticoids….Ketogenic

Increase *in stress*

Case Number 1

26 year old lady: history of weight gain and hypertension.

On Examination:

BP: 170/120mmHg

Obese,

Pigmented.

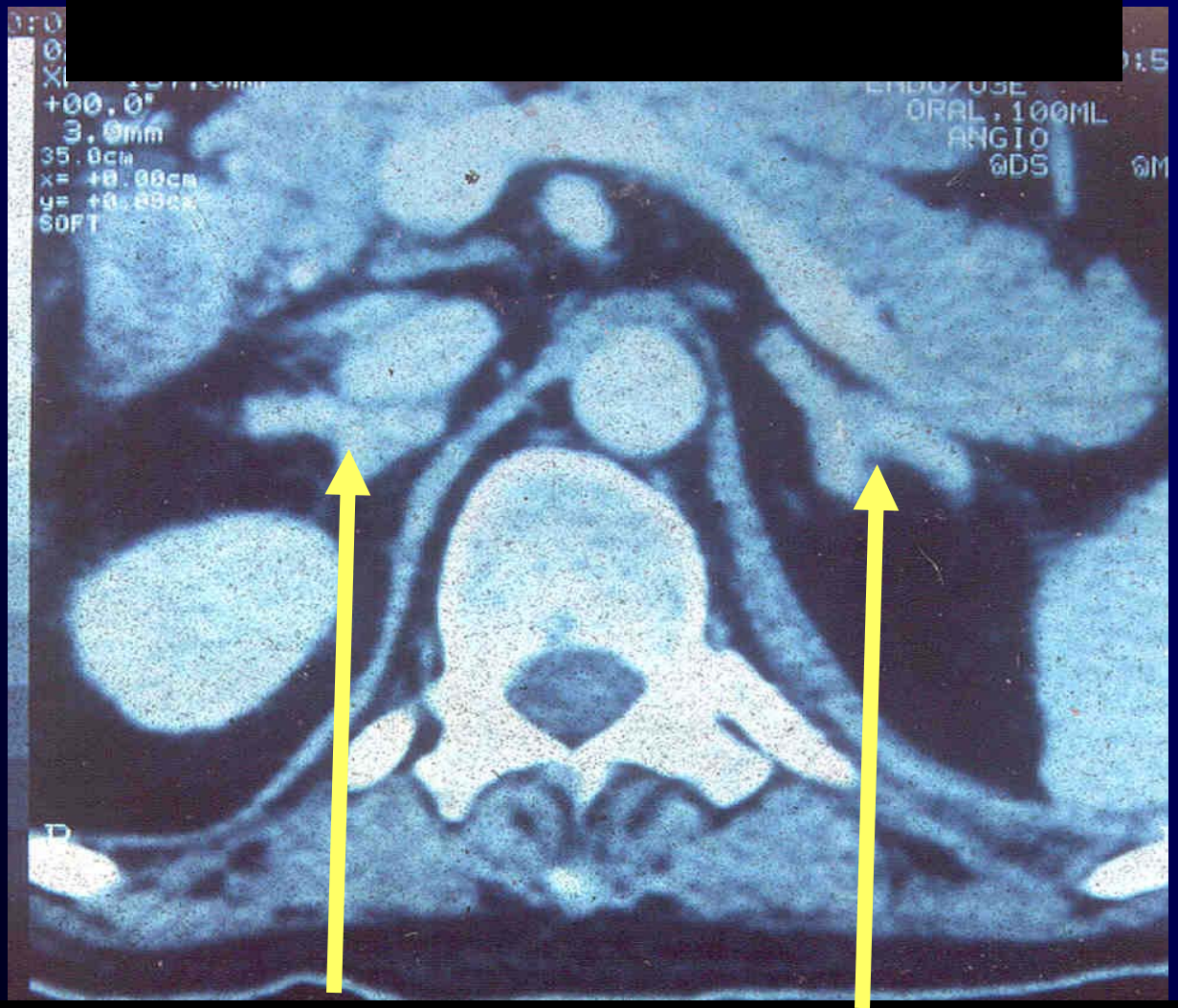
Severe Proximal Myopathy

***8:00AM Cortisol: 36ug/dl .**

Post Dexa 2mg: 7ug/dl

ACTH: 60pg/dl (20-40pg/dl)

MRI pituitary- microadenoma



Bilateral Adrenal Hyperplasia

Glycaemic Profile-Preoperatively

Fasting- 240mg/dl

2hour post breakfast- 320mg/dl

2hour post lunch- 420mg/dl

2hour post dinner- 320mg/dl

****

<u>Mechanistic Viewpoint</u>

Reduced insulin post-receptor activity

Inhibition of GLUT-4 activity

Increased gluconeogenesis (by activation of PEPCK)

Increased production of glucagon

Glycaemic Profile-Preoperatively

Fasting- **240mg/dl**

2hour post breakfast- **320mg/dl**

2hour post lunch- **420mg/dl**

2hour post dinner- **320mg/dl**

****

Mechanistic Viewpoint

Reduced insulin post-receptor activity

Inhibition of GLUT-4 activity

Increased gluconeogenesis

(by activation of PEPCK)

Increased production of glucagon

Trans-sphenoidal Surgery

Glycaemic Profile -Postoperatively

1 week

Fasting- 140 mg/dl

2hour post breakfast- 330 mg/dl

2hour post lunch- 300 mg/dl

2hour post dinner- 280 mg/dl

****

6 weeks

Fasting- 120 mg/dl

Post-prandial 2hour- 240 mg/dl

Case Number 2

…….WITH UNDERLYING

1) Manic depressive psychosis: - 20 years
Stable on Lithium 900mg, CBZ 800mg

2) Tardive Dyskinesia:- 8 years
Secondary to previous phenothiazine therapy.
On Levodopa and trihexyphenidyl

3) Hypertension:- 10 years on Perindopril 4mg

4) Diabetes Mellitus:- for 3 years on Glimiperide 4mg

Current problems……...

Enlarged hands and feet for 4 years,
noted recently by psychiatrist.

Increased diaphoresis.
No tremors, palpitations weight alteration.
No other symptoms of hypopituitarism.
No headaches or symptoms of mass effect.

(contd)…

…….menopausal for 5 years,

occasional hot flushes.

Married 23 years ago.

2 children aged 19 and 17.

On examination…

Middle aged lady:

Weight: 64kg , Height 164cm.

Acromegalic features. Hallux valgus.

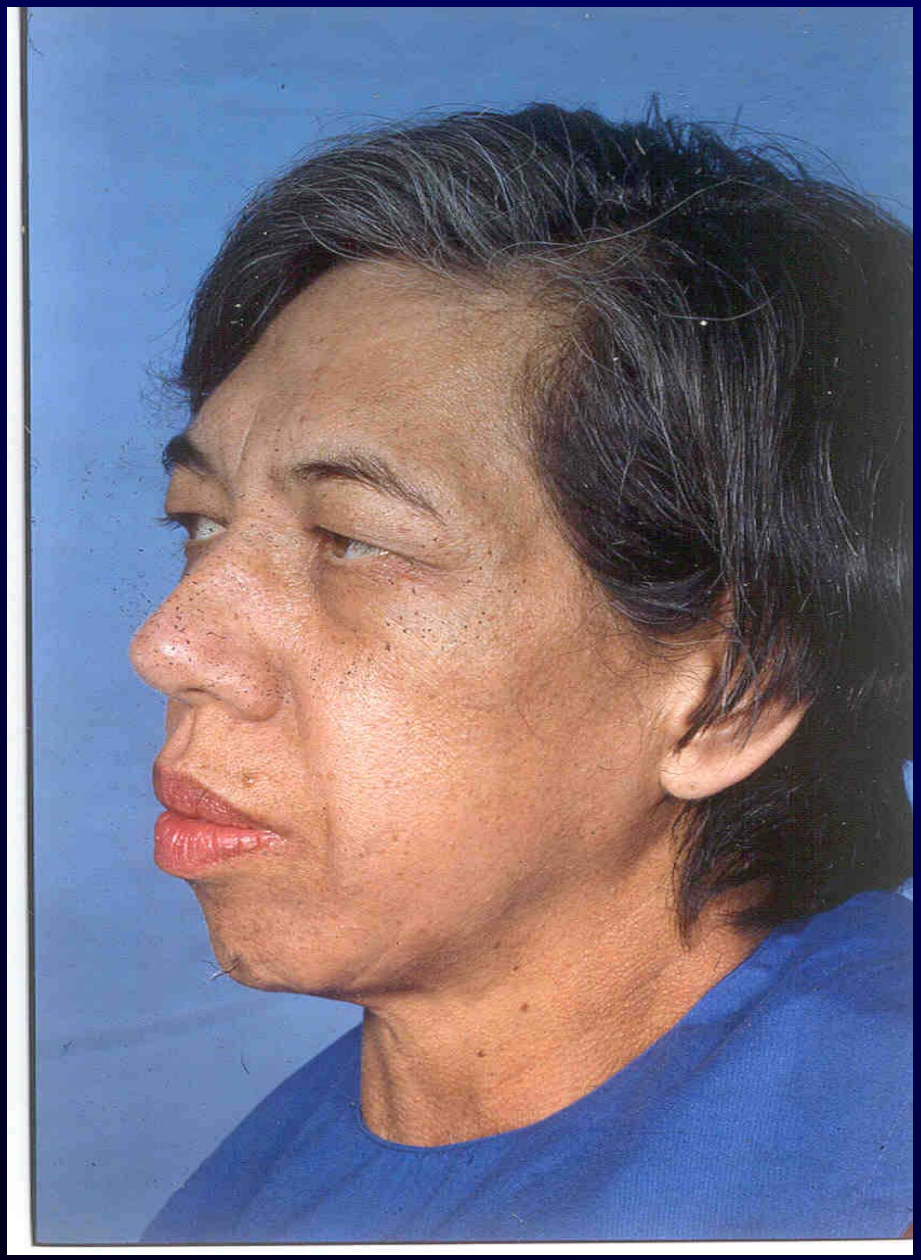
No visual field defects.

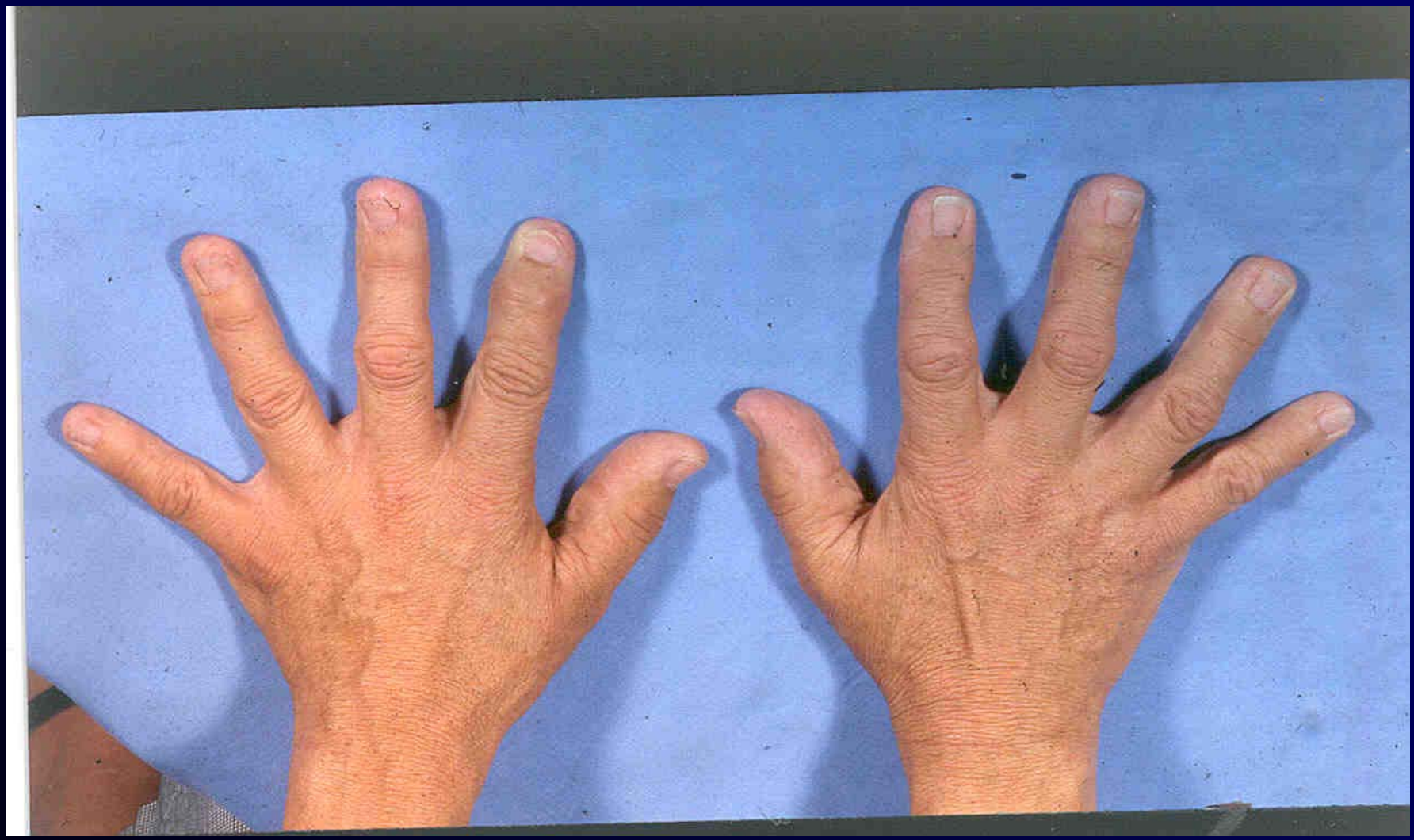
Pulse rate: 84/min and regular

Blood pressure: 130/90mmhg

Generalised coarse tremor present

Dystonic neck movements.





Investigation profile…….

CBC: normal

Biochemistry:

Na: 140meq/l, K: 4.6meq/l

Creat:1.2mg/dl Ca:10.1mg/dl

Phos:3.1mg/dl

Alb:4.2g/l.

Alkaline Phosphatase:290 U/l.

SGPT:42U/l. SGOT: 48U/l.

Fasting Sugar: 190mg/dl

Post prandial: 260mg/dl

Endocrine Tests

IGF-I: 159nmol/l	**(12.8-51)**
GH:140ng/dl at 60min post glucose	**(0-10)**
FSH: 4.6mIu/l	
LH: 0.5mIu/l	
Free T4: 3.1 ng/l	**(0.8-2.0)**
TSH : 1.7mIu/ml	**(0.5-4.5)**
Prolactin: 32.5ng/ml	**(<25ng/l)**


R
sel 90
1 SAT
TR 405.0
TE 12.0/1
TA 04:44
AC 3
SP 37.2
FoV 120*160
Cor
W 968
C 342


24-MAR-1948
12:0
19-
998
IMA
STUDY 3
MF 1.25
A
sel 90
*R
1 SAT
TR 400.0
TE 12.0/1
TA 06:11
AC 2
SP 22.8
SL 3.0
FoV 160*160
230 *256o
W 1016
C 330

Summary of Diagnoses….

1. Pituitary macroadenoma:
   plurihormonal:GH+TSH

2. Diabetes and Hypertension due to GH exc

Management…….

Preoperative therapy:

Octreotide 100 IU tds and

Carbimazole 30mg per day

After 1 week on therapy with Octreotide:

T4: 1.8ng/dl

IGF-I: 141nmol/l

Fasting Sugar: 65mg/dl

Post-Prandial Sugar: 130mg/dl

Glimiperide stopped

****

Mechanistic Viewpoint

Octreotride reduces growth hormone as a Somatostatin analogue leading to a normalization of sugars.

After 1 week on therapy with Octreotide:

T4: 1.8ng/dl

IGF-I: 141nmol/l

Fasting Sugar: 65mg/dl

Post-Prandial Sugar: 130mg/dl

Glimiperide stopped

****

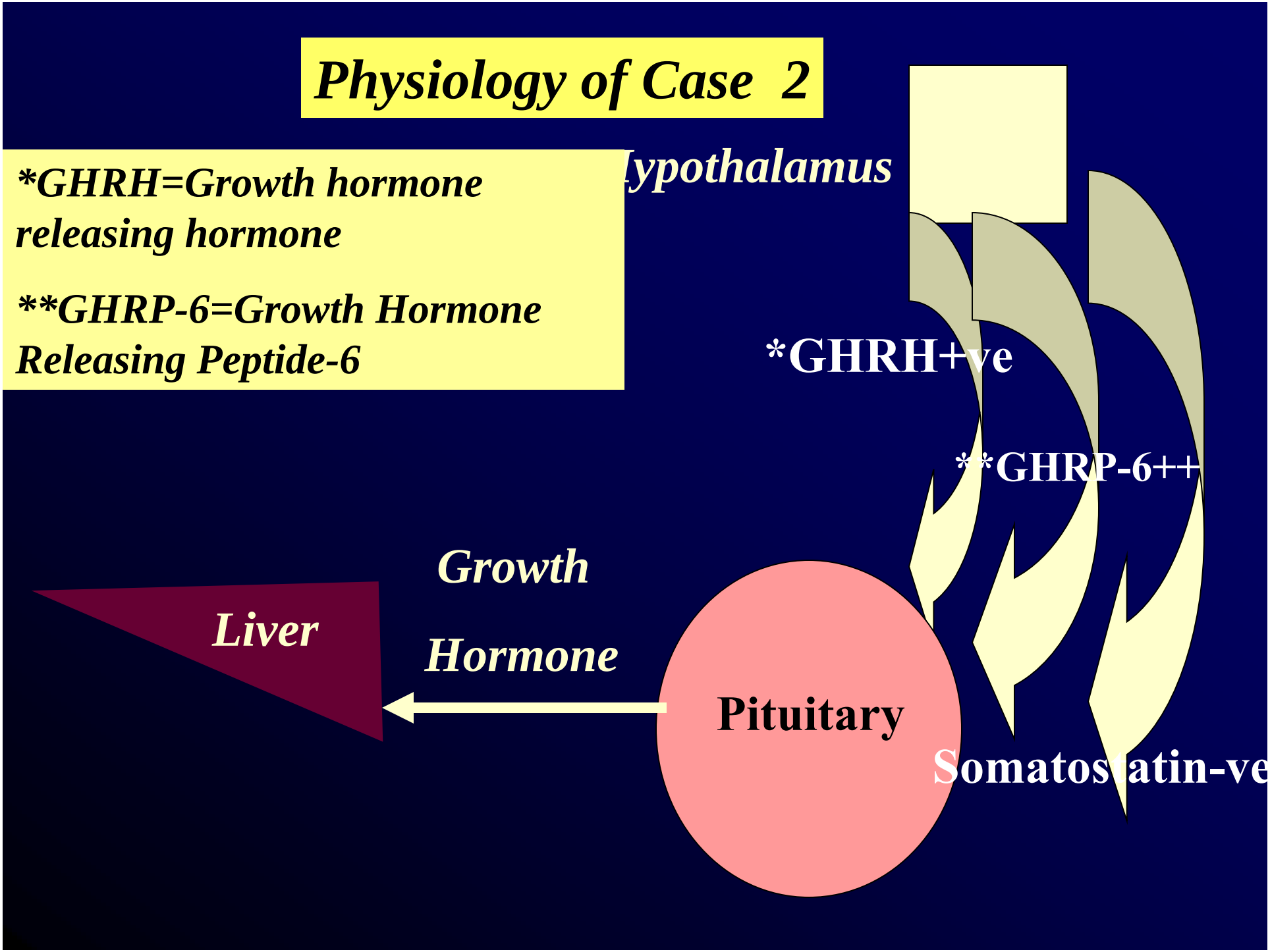
Mechanistic Viewpoint

Octreotride reduces growth hormone as a Somatostatin analogue leading to a normalization of sugars.

Physiology of Case 2

**GHRH=Growth hormone releasing hormone*

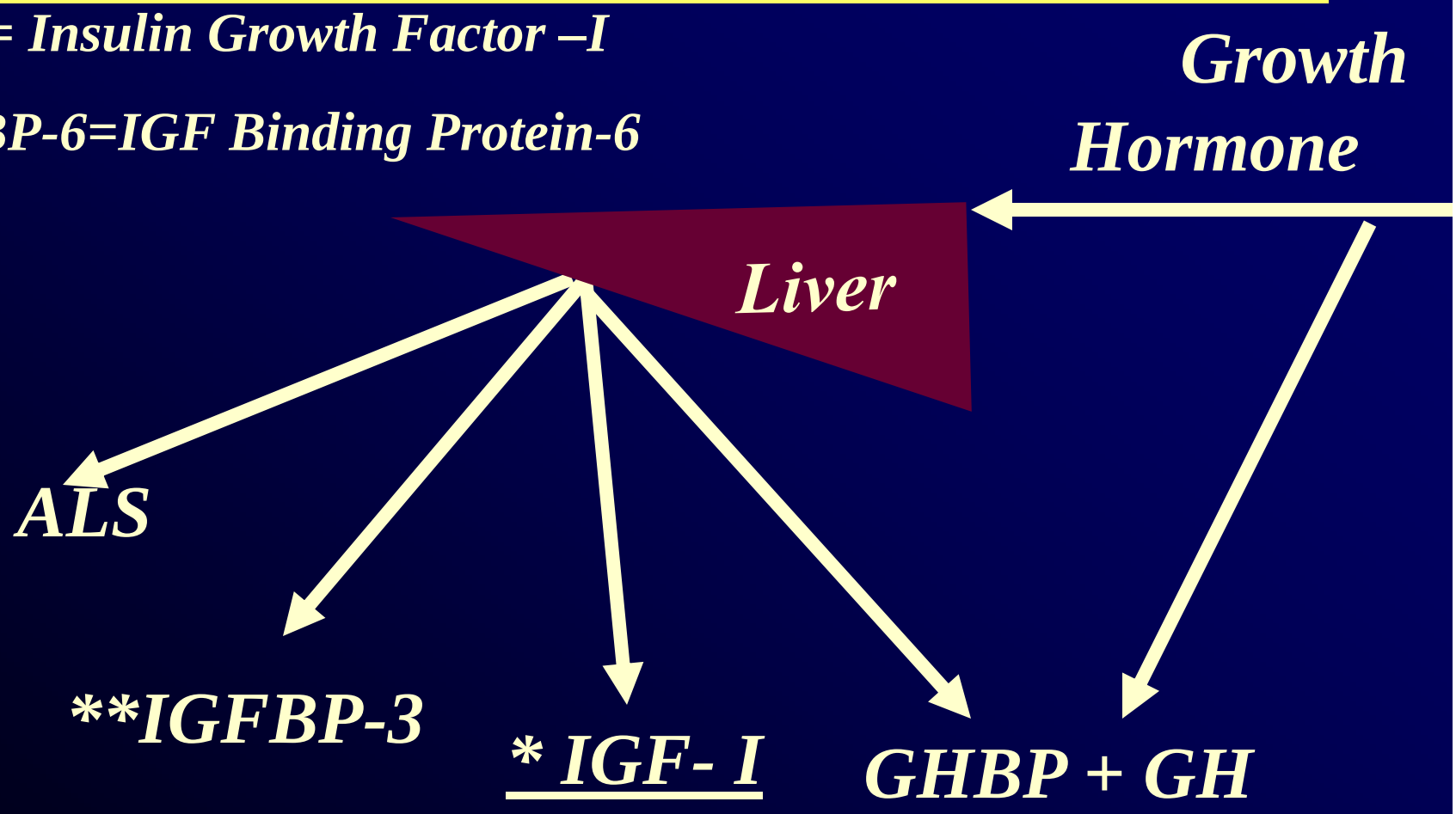
***GHRP-6=Growth Hormone Releasing Peptide-6*



Growth factors

**IGF-I= Insulin Growth Factor –I*

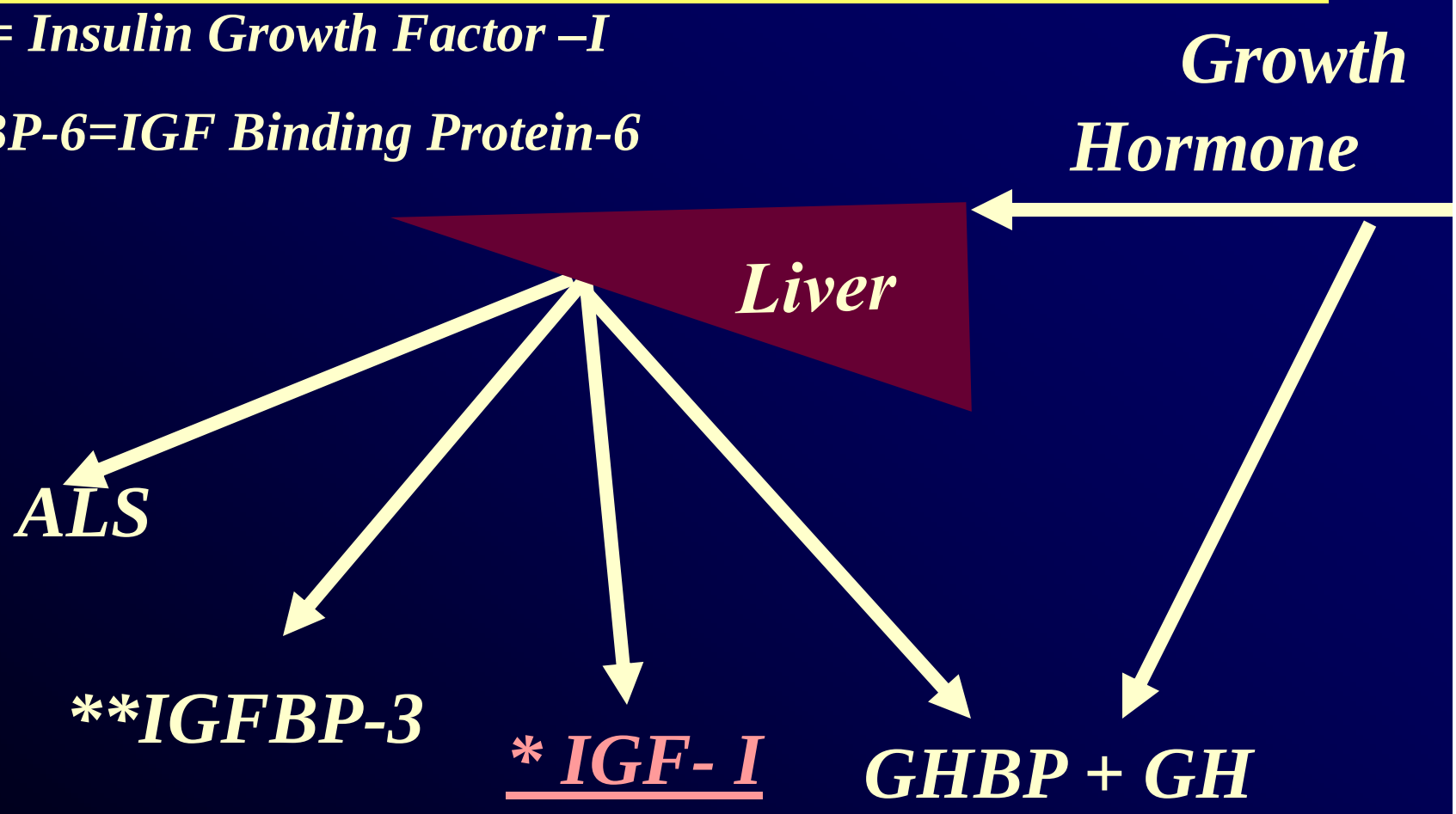
***IGFBP-6=IGF Binding Protein-6*



Growth factors

**IGF-I= Insulin Growth Factor –I*

***IGFBP-6=IGF Binding Protein-6*

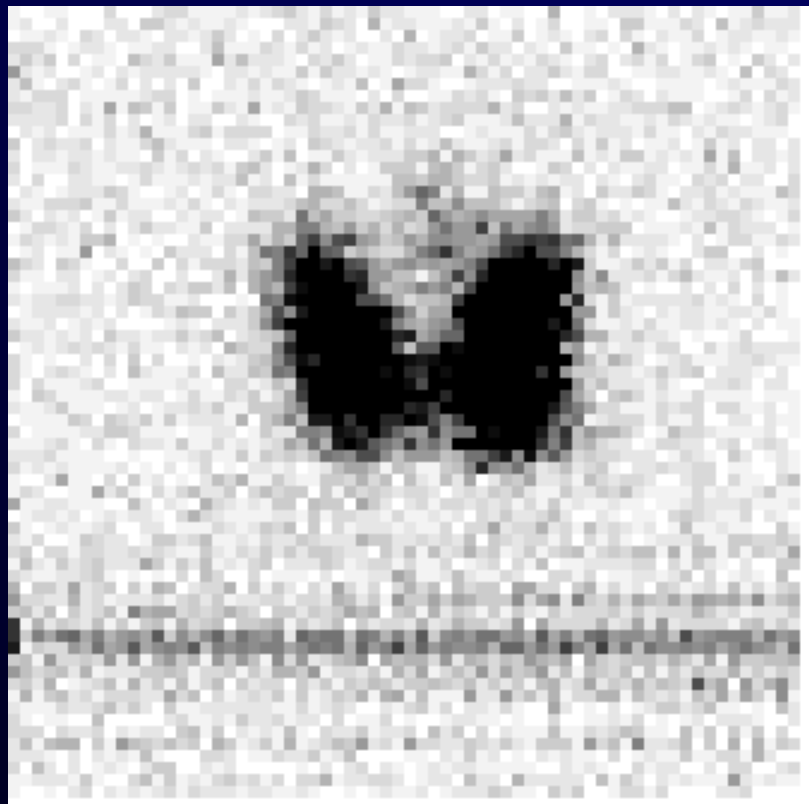


Case Number 3

Symptoms sweating, prominence of eyes:

tremors, palpitations.

T4: 24ug/dl **TSH: <0.001**



Symmetrical enlargement & uniform uptake
2 hours: 40%, 6 hours: 54%, 24Hours: 80%

Glycaemic Profile in thyrotoxicosis (Off medications)

Fasting- 50 mg/dl

2hour post breakfast- 260 mg/dl

2hour post lunch- 240 mg/dl

2hour post dinner- 210 mg/dl

****

<u>Mechanistic Viewpoint</u>

Increased/ More rapid Postprandial absorption

Glycogenolysis/ gluconeogenesis increased:

Glycaemic Profile in thyrotoxicosis (Off medications)

Fasting- 50 mg/dl

2hour post breakfast- 260 mg/dl

2hour post lunch- 240 mg/dl

2hour post dinner- 210 mg/dl

****

Mechanistic Viewpoint

Increased/ More rapid Postprandial absorption

Glycogenolysis/ gluconeogenesis increased:

Glycaemic Profile (Off medications)

Fasting- 50 mg/dl

2hour post breakfast- 260 mg/dl

2hour post lunch- 240 mg/dl

2hour post dinner- 210 mg/dl

****

Mechanistic Viewpoint

Increased/ More rapid Postprandial absorption

Glycogenolysis/ gluconeogenesis increased

But……..glycogen storage is reduced markedly

Glycaemic Profile (On medications)

Fasting- 111 mg/dl

2hour post breakfast- 160 mg/dl

2hour post lunch- 24mg/dl

2hour post dinner- 35 mg/dl

On Neomercazole: 30mg per day.

****

<u>Mechanistic Viewpoint</u>

1) Thionamides (Neomercazole) may have an affinity for the sulphonylurea receptor

2) Autoimmune hypoglycaemia

(antibodies to the insulin receptor)

Glycaemic Profile (On medications)

Fasting- **111 mg/dl**

2hour post breakfast- **160 mg/dl**

2hour post lunch- **24mg/dl**

2hour post dinner- **35 mg/dl**

On Neomercazole: 30mg per day.

****

Mechanistic Viewpoint

1) Thionamides (Neomercazole) may have an affinity for the sulphonylurea receptor

2) Autoimmune hypoglycaemia (antibodies to the insulin receptor)

Case Number 4

27 year old lady, presents with:

Palpitations, headache and weight loss of 8 kg over a period of 6 months.

On examination:

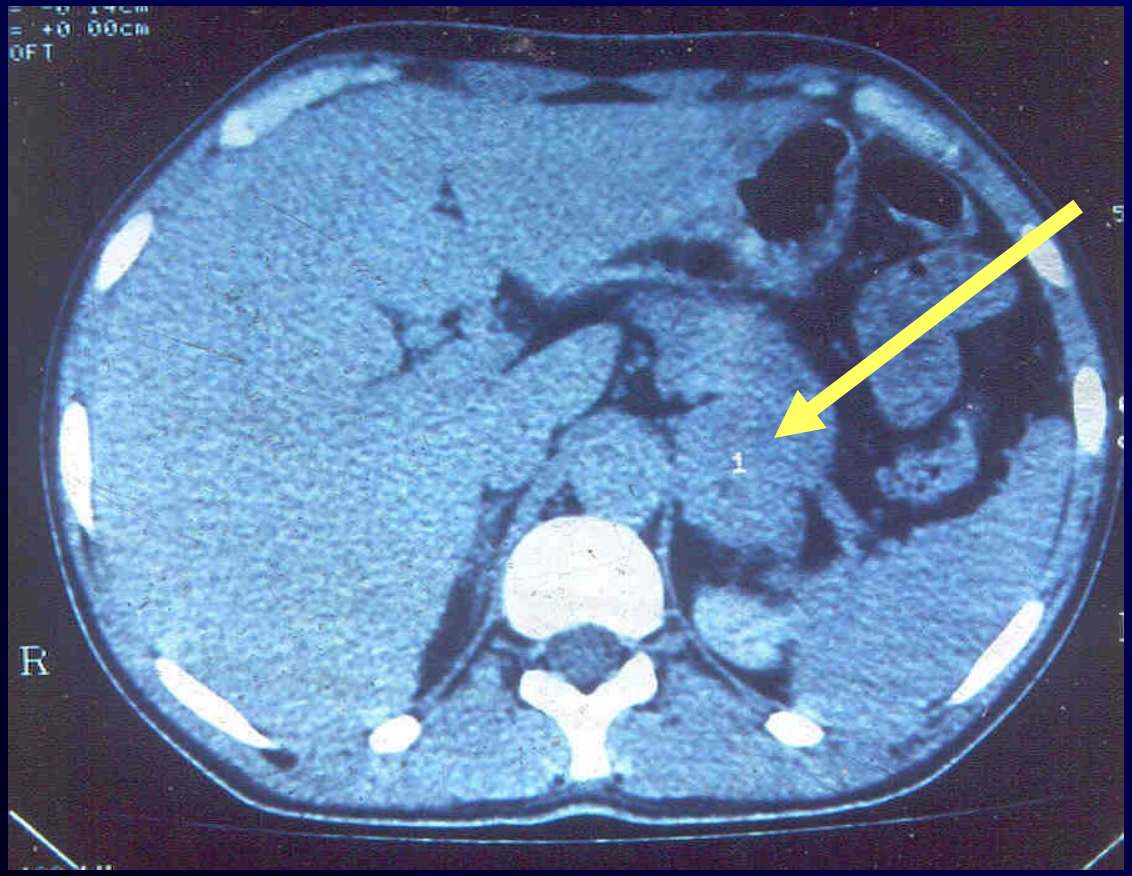
Weight: 40 kg Height 152 cm

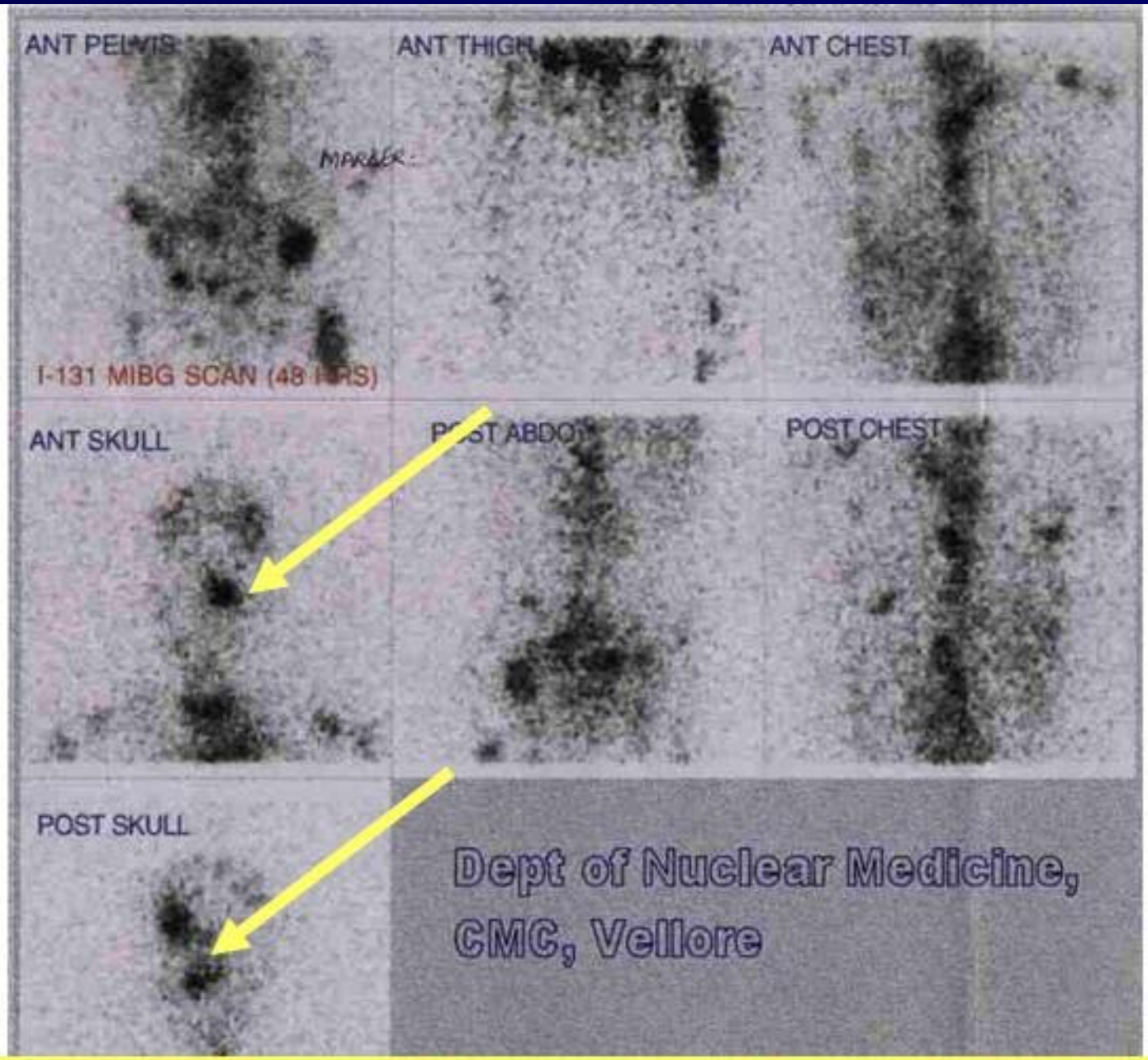
Blood pressure: 240/130mmHg

Optic Fundus: Grade III hypertensive changes

24 Hour Urinary VMA: 22mg in 24 hours (N:7mg)

Extra-adrenal Phaeochromocytoma





Metastases Base of Skull

Glycaemic Profile

Fasting- 110mg/dl

2hour post breakfast- 200 mg/dl

2hour post lunch- 230mg/dl

2hour post dinner- 264 mg/dl

On Amlodipine: 10mg/ day and Losartan 50mg twice daily

<u>Mechanistic Viewpoint</u>

Excessive Catecholamines cause:

1) Alpha adrenergic effect-reduced insulin secretion

2) Beta adrenergic effect-increased hepatic glycogenolysis

3) Increased circulating fatty acids: insulin resistance

Glycaemic Profile- on modified therapy

Fasting- 110mg/dl

2hour post breakfast- 134 mg/dl

2hour post lunch- 110mg/dl

2hour post dinner- 192 mg/dl

On Amlodipine: 10mg/ day and Losartan 50mg twice daily

Prazocin XL: 10mg twice daily

<u>Mechanistic Viewpoint</u>

Alpha adrenergic blocking effect

- increased insulin secretion

Oral Hypoglycaemic agents not used.

Glycaemic Profile- Post-operative tumour excision

6 hours postoperatively: 54 mg/dl

****

Mechanistic Viewpoint

1) **Sudden catecholamine withdrawal**
2) **Depleted Hepatic glycogen storage**

Differential Diagnosis of Phaeo

Anxiety/ Panic Attacks*

Hyperthyroidism

Paroxysmal Atrial Tachycardia*

Menopause*

Vasodilating headache*

Diabetic Autonomic Neuropathy/ Porphyria/GBS

Intracranial Lesions

Diencephalic Seizure

Carcinoid

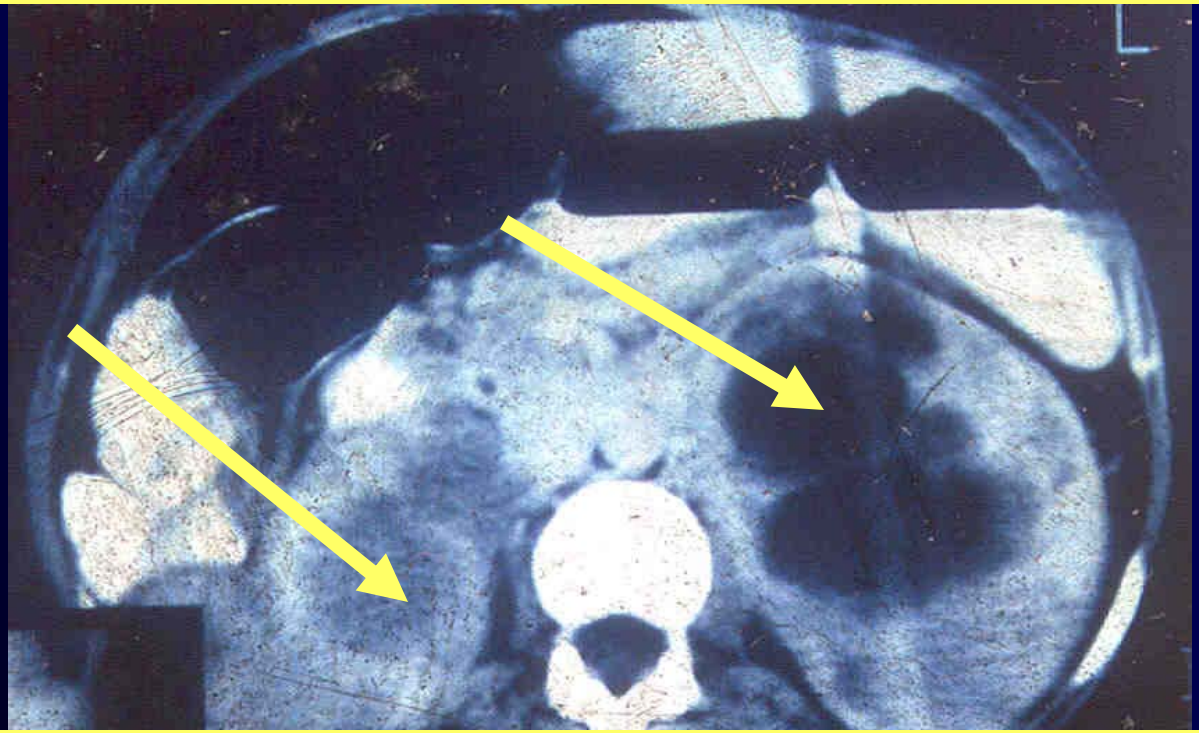
Monoamine Oxidase inhibitors

Hypoglycaemia*

Mastocytosis

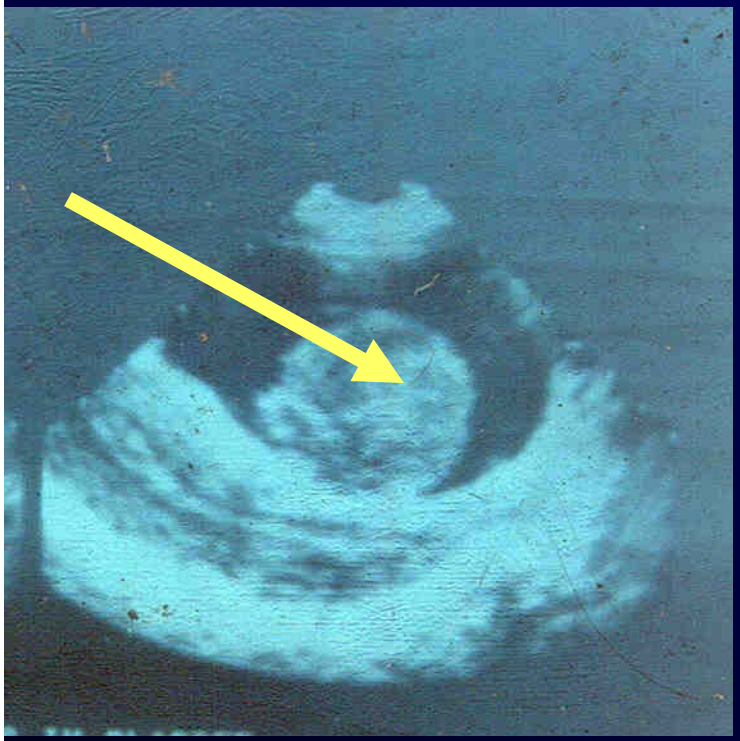
Tricyclics, Ephedrine, PCP, LSD

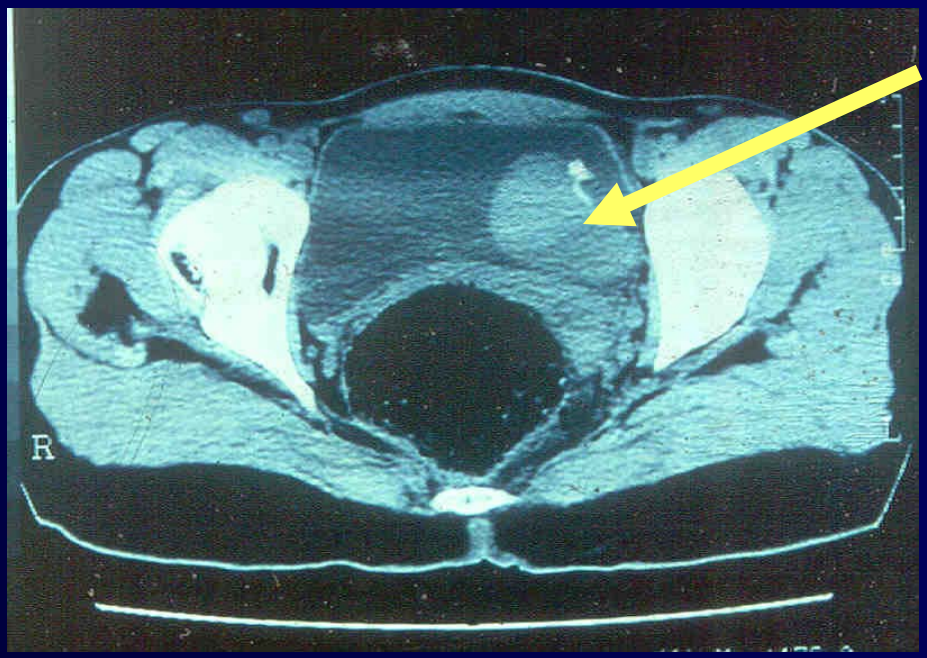
Bilateral Adrenal Phaechromocytomas With Hypertension and Diabetes



Required insulin for therapy

Intravesical Phaeo





Required insulin for therapy

Summarizing, The Endocrine Causes for Secondary Diabetes……

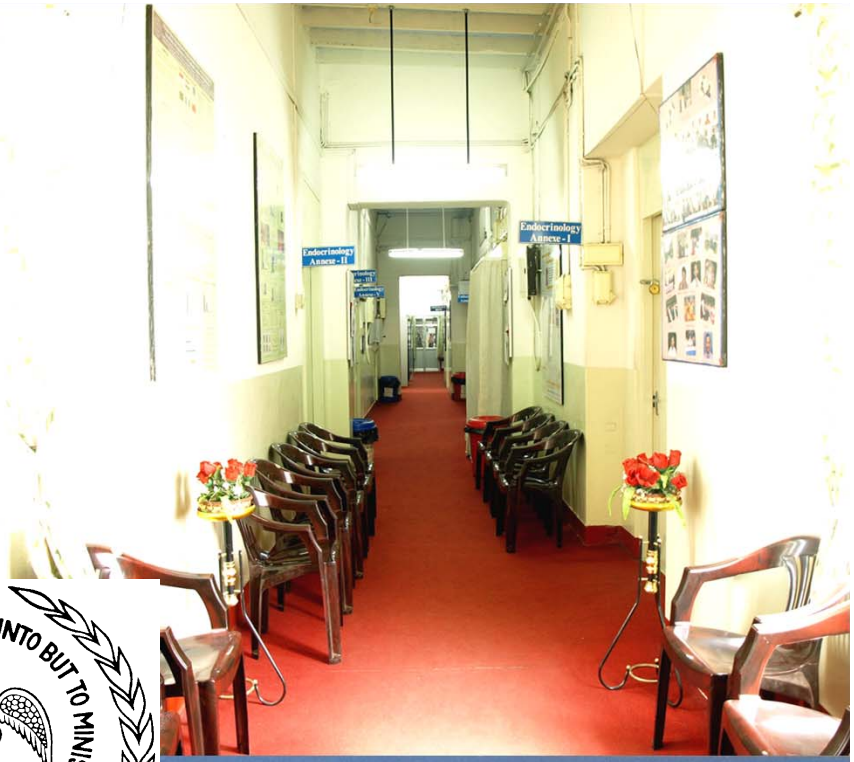
1. Growth Hormone - Acromegaly
   -Treatment
2. Corticosteroid Excess -Exogenous
   -Endogenous
3. Hyperthyroidism
4. Phaeochromocytoma
5. Glucagonoma Syndrome
6. Somatostatinoma Syndrome

Summarizing……

1. **Post-prandial hyperglycaemia is a dominant phenomenon in Endocrine disorders for secondary diabetes.**

2. **Reversal of hyperglycaemia- as a natural phenomenon or as a post-therapeutic adjunct is a common occurrence.**

3. **Spontaneous Hypoglycaemia due to various mechanisms may occur- both fasting and postprandial.**



NOT TO BE MINISTERED UNTO BUT TO MINISTER
CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA

Thank You