PITUITARY FUNCTION TESTS: An Overview

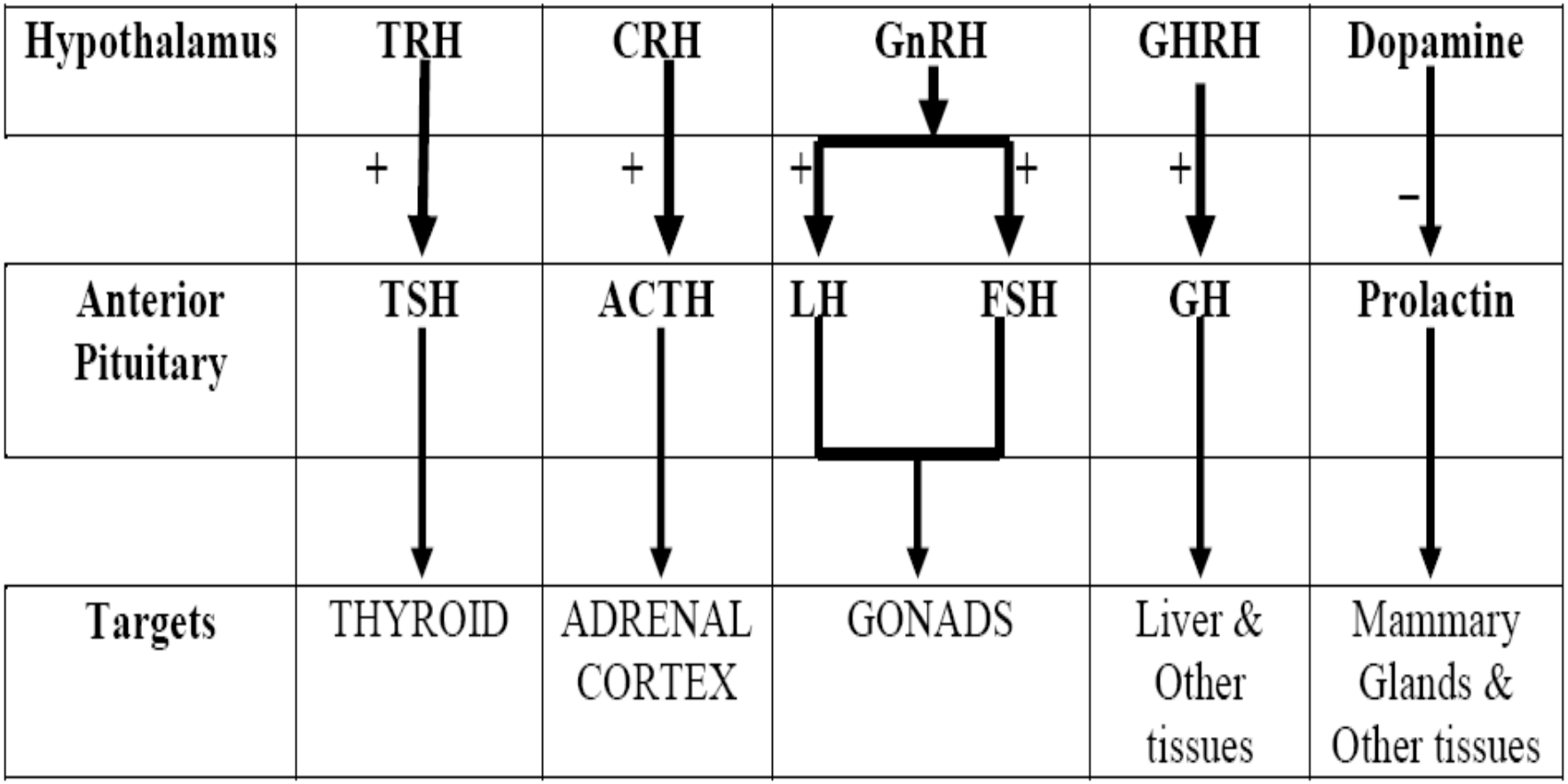
University of Papua New Guinea
School of Medicine & Health Sciences,
Division of Basic Medical Sciences,
Discipline of Biochemistry & Molecular Biology,
PBL MBBS III

VJ Temple

Pituitary Function General Consideration

- Release of all Pituitary Hormones is Episodic; it reflects the Pulsatile secretion of Hypothalamic Releasing Factors;
- Slower Diurnal Rhythms in secretion are superimposed upon episodic patterns;
  - Important to understand and consider these patterns when assessing Pituitary Function;
- To assess functional state of Pituitary Gland it is important to:
  - Use simple screening tests to eliminate other courses, before using more complicated Dynamic Tests;
- If Pituitary disorder is suspected, then damage to Pituitary Functions should be assessed;

Fig. 1: Hypothalamic-Anterior Pituitary Axis: Showing Releasing Hormones and corresponding Anterior Pituitary hormones



How is Pituitary Function Assessed?

- If Hypopituitarism is suspected in a patient, combined Pituitary Function Test (**PFT**) should be requested;
- **Combined PFT is used to assess the Anterior Pituitary reserve for production of Anterior Pituitary Hormones**
  - **ACTH,**
  - **GH,**
  - **FSH,**
  - **LH,**
  - **TSH;**
- Combined Pituitary Function Tests include:
  - **TRH / GnRH / GHRH / CRH Tests;**

- Blood is collected to measurement the following:
  - Blood Glucose,
    - To assess Hypoglycemic response during the test;
  - Basal plasma levels of:
    - FSH,
    - LH,
    - Estradiol (in female patients)
    - Testosterone (in male patients),
    - Cortisol,
    - TSH,
    - FT4,
    - HGH,
    - Prolactin;

- Patient is given **IV infusions** from separate syringes:
  - **Insulin (0.10U/kg),**
  - **TRH (200ug),**
  - **GnRH (50ug),**
- Blood samples are collected at intervals of:
  - **0, 20, 30, 60, 90 and 120 minutes for assay of the respective hormones;**
- **NB: PFT must be carried out in the presence of a Clinician;**

- Throughout the duration of the tests the following must be available for IV administration if needed:
  - Glucose solution,
  - Hydrocortisone,
- Insulin-Induced Hypoglycemic Test MUST be replaced by the GHRH and CRH test to investigate HGH and Cortisol secretion;

How is the Combined PFT Interpreted? (Figs: 2 – 5)

- Interpretation of the combined PFT follows the same procedure for interpretation of each test when performed separately;
- IMPORTANT TO NOTE:
  - **Request for PFT by Clinicians is on the decrease, because of the availability of more specific and highly specialized tests;**

What are the current biochemical recommendations for assessing Anterior Pituitary Function?

- Current Biochemical recommendations for assessing Anterior Pituitary function:
  - **Measure plasma levels of Basal Anterior Pituitary Hormones;**
  - **Measure plasma level of Hormone produced by the corresponding Primary Target Organ;**
  - Stimulation tests of IV administration of GnRH and TRH are outdated;
  - Exceptions include:
    - Investigations for Acromegaly and Cushing's Syndrome;
      - Stimulation or Suppression tests or both must be done;

Outline the biochemical investigation for initial assessment of a patient with suspected Pituitary Dysfunction

- Biochemical investigations for initial assessment of Pituitary dysfunction: (**First Line methods**):
- Basal measurements for diagnostic information:
  - At 9.00am collect blood sample for basal levels of:
    - Cortisol,
    - TSH & FT4,
    - Testosterone or Estradiol,
    - LH & FSH,
    - Prolactin (ACTH may be included);
  - If Posterior Pituitary dysfunction is suspected then, measure Osmolality in Serum and Urine;

- **Interpretation of the results**:
  - ❖ **Patient with normal stature**,
    - No clinical evidence of Pituitary disease,
    - Normal HPT-axis,
    - Normal HPG-axis,
    - Normal Serum and Urine Osmolality,
    - **Plasma [Cortisol] > 400nmol/L**,
  - **Such results indicate: Normal Pituitary Function**;

- If Plasma **[Cortisol]** is between **100 – 400nmol/L**
  - Then request Synacthen Test to assess HPA-axis;
  - Request for Insulin Stress Test if the result is Equivocal (borderline);
- Patient with strong clinical signs for Pituitary dysfunction (Hypopituitarism) or Abnormal basal results:
  - Request for Insulin Stress Test to assess ACTH and HGH reserve;
    - Do not make request if contraindication in patient is suspected;

- **NB**: If Thyroid hormones and ACTH deficiencies are identified on the basal results, patient should be treated before proceeding with other investigations of Pituitary function; **WHY???**
  - Hypothyroidism reduces ACTH and HGH responses to Insulin Stress Test;

- If basal Osmolality of Urine and Plasma are affected;
  - Request for the Fluid Deprivation Test;

INSULIN STRESS TEST FOR GROWTH HORMONE & CORTISOL

{This test is contraindicated for children and all patients with significant Cardiac problems and for patients with seizures}

What is the Insulin Stress Test (IST)?

- **IST** is also called Insulin Hypoglycemia Test (**IHT**):
- It is use for assessment of:
  - HGH reserve,
  - Hypothalamic-Pituitary-Adrenal Axis (HPA-axis),
  - Investigation of suspected Hypopituitarism in adults and in Stunted children,

What is the procedure for the IST (Figs 2 & 3)?

- Patient should be in supine position;
- IV line inserted into vein in back of hand or arm;
- Blood is collected for baseline levels of:
  - Glucose,
  - Cortisol,
  - HGH;
- Insulin (0.1U/kg) is administered IV,
- Blood samples are collected at intervals of 30, 45, 60 and 90 minutes after IV injection of Insulin;

- Blood samples are used to assess **HGH** and **Cortisol** response to Insulin Induced Hypoglycemic Stress;
- Blood glucose level must be monitored regularly;
  - Insulin is expected to reduce blood glucose level to about **2.2mmol/L or lower**;
- Essential to achieve significant drop in blood glucose needed to Stress the Cerebral tissues, and stimulate the Anterior Pituitary gland;

What are the special precautions needed during the IST?

- Clinician must be present throughout the IST;
- Development of Hypoglycemia by patient may result in discomfort:
  - Shaking,
  - Sweating,
  - Feel Hungry,
  - Tired,
  - Sleepy;
- Glucose injection, should be use to restore the blood glucose to normal if the patient develops severe hypoglycemia;

How are the results of IST Interpreted?

- Results of IST should be rejected if hypoglycemia (2.2mmol/L or lower blood glucose level) was not achieved during the test;

❖In apparently healthy individuals, Hypoglycemia causes:

- Increase in Plasma [HGH] to more than 20m U/L;
- Plasma [Cortisol] increases to maximum (about 425nmol/L) in 60 to 90 minutes;

❖In patient with Partial Pituitary Failure, Hypoglycemia causes:

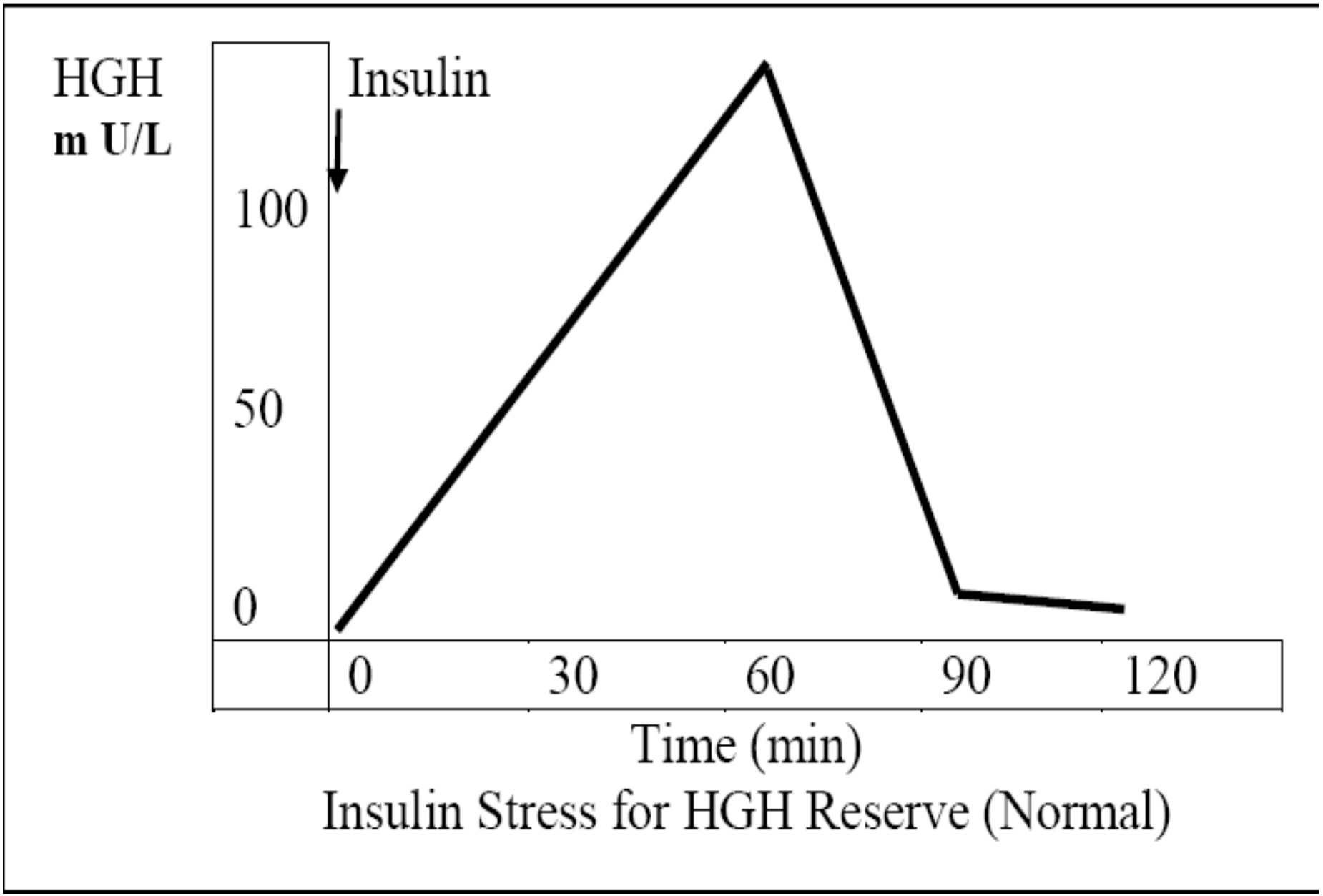
- Limited increases in Plasma [HGH],
- Limited increase in plasma [Cortisol];

❖In patients with Severe Pituitary Dysfunction, Hypoglycemia has limited effect:

- Plasma [HGH] does not increase significantly;
- Plasma [Cortisol] does not increase significantly;

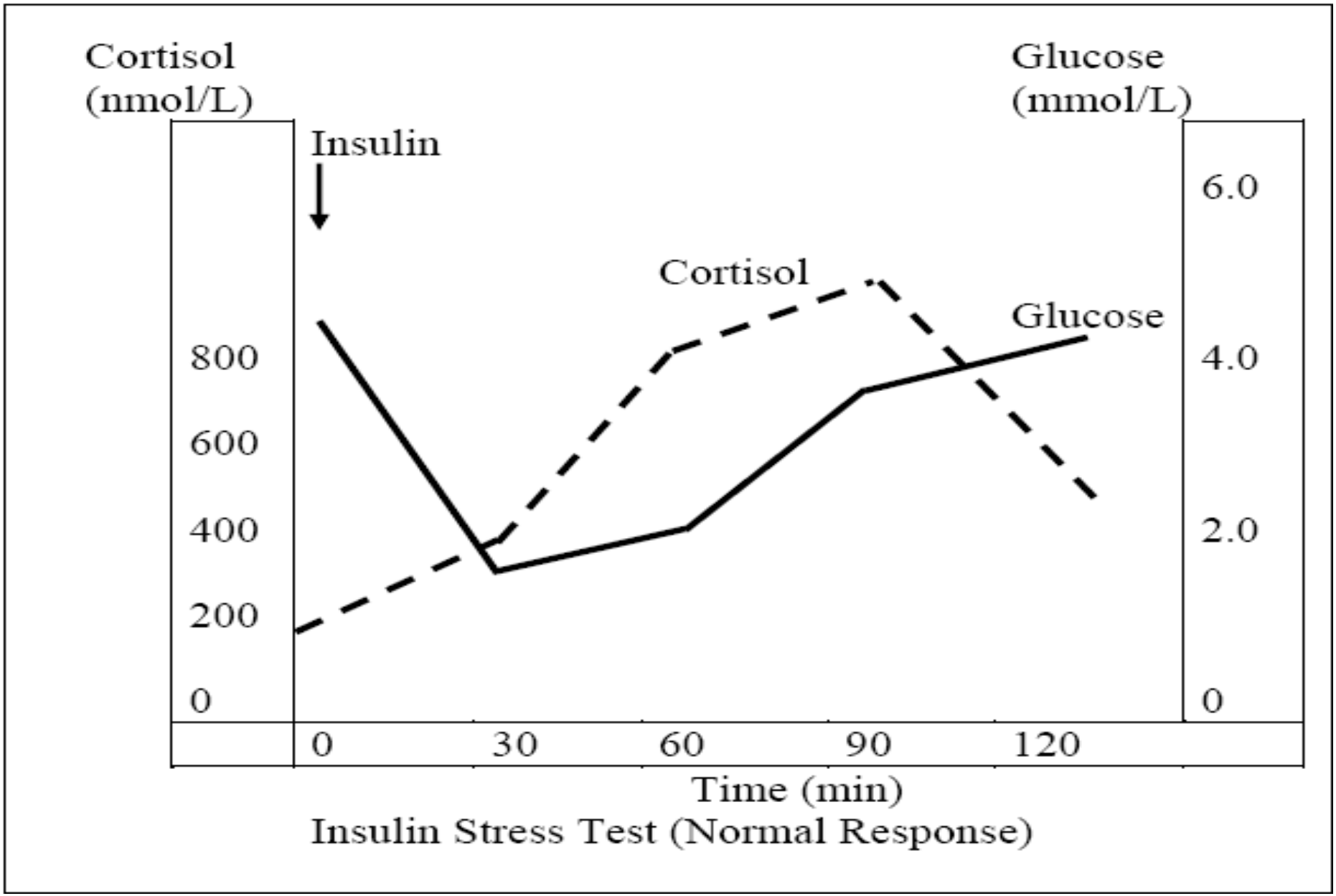
- Pre-menopausal women, the test can be performed at any phase of the menstrual cycle, because there are no cycle effects on the HPA-Axis response to Insulin-Induced Hypoglycemia;
- **NB:** Both male and female children show subnormal responses to Hypoglycemia and other Dynamic Tests just before Puberty;

Fig. 2:



Insulin Stress for HGH Reserve (Normal)

Fig. 3: Insulin Stress Test for Cortisol reserve



How does high plasma Cortisol affect Pituitary Function Tests?

- High plasma Cortisol suppresses:
  - Hypothalamus,
  - Pituitary Gland;
  - LH response to GnRH;
  - TSH response to TRH;
- High Plasma Cortisol negatively affects increase in Plasma [HGH] in response to induced Hypoglycemia;
- **NB**: Adrenocortical Hyper-function (Cushing's syndrome) causes release of High Cortisol in Plasma, thus PFT results will not be interpreted correctly;

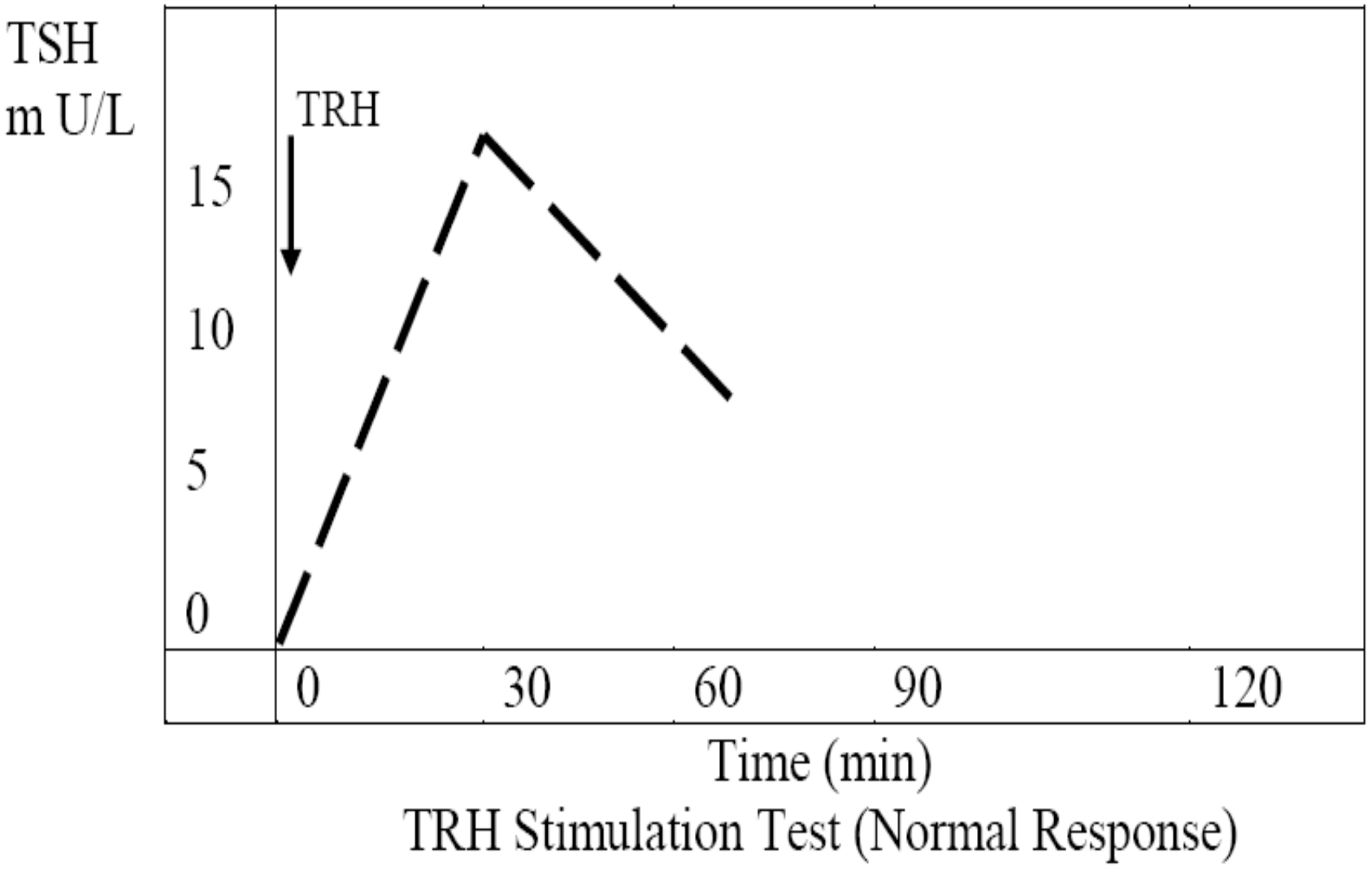
What is the procedure for the TRH test (Fig. 4)?

- Patient should be in supine position;
- IV line inserted into vein in back of hand or arm;
- Collect blood for baseline level of **TSH** and **FT4**;
- Give calculated amount of TRH to stimulate the Anterior Pituitary;
- Collect blood at 20 and 60 minutes after TRH injection;
- Measure **TSH** and **FT4** levels in blood samples;

How are the results of the TRH test interpreted?

- Plasma [TSH] increases after injection of 200mcg TRH
- TRH test can exclude Hyperthyroidism in borderline cases or where Plasma [FT4] and [FT3] are equivocal;
- Plasma [TSH] above reference excludes Hyperthyroidism,
- Absent or Impaired TSH response is consistent with:
  - Hyperthyroidism; Grave's ophthalmology,
  - Some Euthyroid Multi-nodular Goiters,
  - Subclinical Toxic Adenoma,
  - Acromegaly, Hypopituitarism, Cushing's disease,
- TSH may be impaired if too much Thyroid hormones are given to Hypothyroid patients;
- **NB:** TRH stimulation test has largely been replaced by the highly sensitive TSH assays;

Fig. 4:



TRH Stimulation Test (Normal Response)

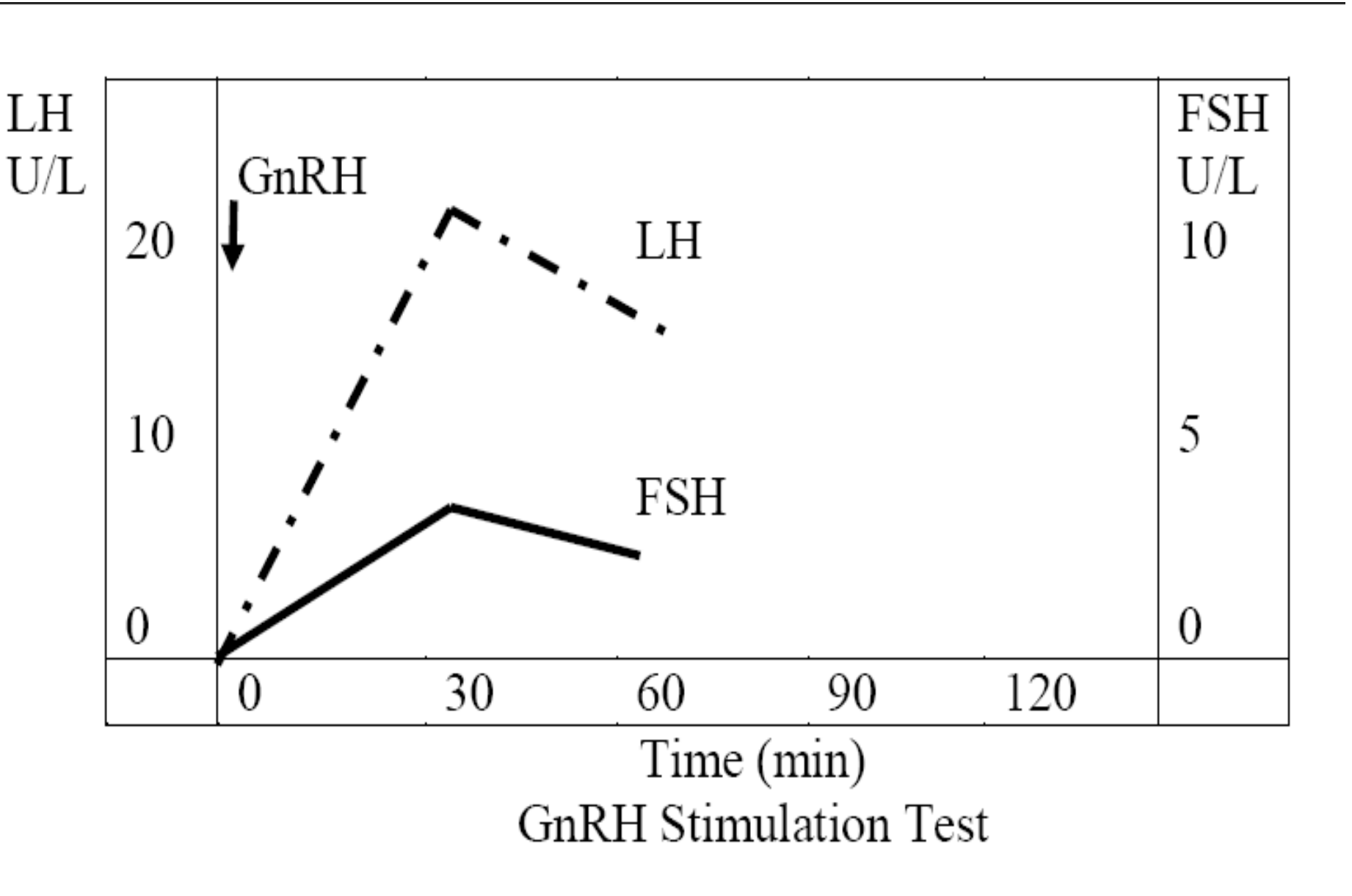
What is the procedure for the GnRH TEST? (Fig. 5)

- GnRH test involves infusion of GnRH and assay at timed intervals of LH, FSH and sex steroid (Estradiol, or Testosterone);
- Patient should be in supine position;
- IV line inserted in vein in back of hand or arm;
- Collect blood for base line levels of **LH**, **FSH**, and the appropriate Sex steroid hormone,
- Give calculated amount of GnRH;
- Collect blood samples at 30 and 60 minutes after the GnRH injection;
- Measure **LH**, **FSH** and appropriate Sex hormone;

How are the results of the GnRH test interpreted?

- Interpretation should be made in the context of the pubertal stage;
- If there is no response then Gonadotrophin deficiency might be suspected;
  - However this may be unreliable in Pre-Pubertal children, including Uncomplicated Pubertal Delay;
- Exaggerated response may be seen in Precocious Puberty, or in conditions where there is end organ failure to respond - such as Turner's syndrome;

Fig. 5:


LH
U/L
GnRH
20
10
0
LH
FSH
FSH
U/L
10
5
0
0
30
60
90
120
Time (min)
GnRH Stimulation Test

What is fluid deprivation test?

- Fluid Deprivation Test:
  - Test to check regulation of fluid balance and power of the kidney tubules to concentration the urine;
    - Regulation of fluid balance involves Arginine Vasopressin (AVP) produced in Posterior Pituitary;
  - Test must be done only under medical supervision as it can potentially cause dehydration, fluid and salt imbalance;

What is the procedure for the Fluid Deprivation Test?

- Test carried out after overnight fasting with no fluid intake;
- Collect blood and urine at 09.00am;
- Allow patient to consume only dry foodstuff without any fluid up until 4.00 pm;
- Obtain Body weight of patient,
- Measure Urine output every hour;
- Collect blood samples every hour;

How is the fluid deprivation test results interpreted?

- **Healthy individuals**:
  - Hourly urine output will drop and will become more concentrated due to lack of fluid intake;
  - Body weight and blood concentration will remain the same;
- **Patient with Diabetes Insipidus due to lack of AVP:**
  - Production of large volume of urine continues despite no intake of water;
  - Urine remains diluted, body weight falls and blood become more concentrated as they become dehydrated;

- **Additional procedure**:
  - At 4.00pm DDAVP (1-Deamino, 8-D-Argenine Vasopressin; structurally similar to natural AVP) will be injected and patient allowed to take fluid;
  - Urine and blood collections will continue up until 20.00hr;
- Aim is to assess body's response to lack of fluids and the response after injection of DDAVP;

Further Interpretation of results

- Results may be interpreted as:
  - Urine Osmolality less than 300mosmol/kg after fluid deprivation, and Greater than 800mosmol/kg after Desmopressin suggests **Cranial Diabetes Insipidus**;
  - Urine Osmolality less than 300mosmol/kg after fluid deprivation, and Less than 300mosmol/kg after Desmopressin suggests **Nephrogenic Diabetes Insipidus**;
  - Urine Osmolarity greater than 800mosmol/kg after fluid deprivation, and Greater than 800mosmol/kg after Desmopressin suggests **Primary Polydipsia**;

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