ENDOCRINE PANCREAS: DM

● Diabetes mellitus (DM) is a ***group of metabolic disorders*** *sharing a* ***common*** *underlying feature* → ***hyperglycemia*****,**

results from defects in insulin secretion, action, or both.

● DM affects **7% of the US population (**21 millions), 1/3 of whom are undiagnosed! And at least 1 /3 (33%) of the Jordanian!

● DM is a leading cause of :

1)**end-stage renal** disease,

2) Adultonset **blindness**

3) lower extremity **amputation.**

4) It greatly ↑ the risk of developing MI & IHD & CVA (

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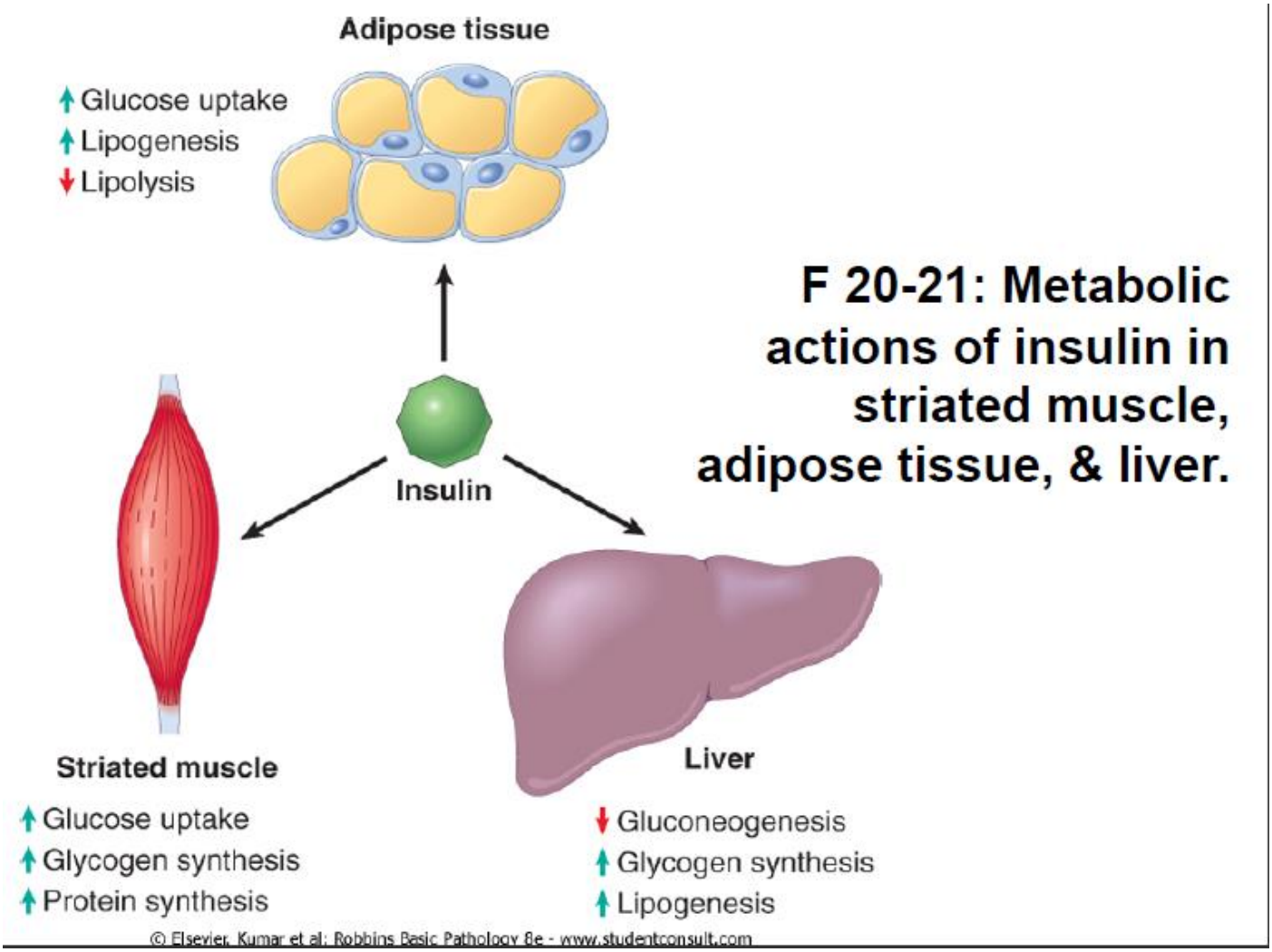
Types of DM:

● ***Type 1DM***	●***Type 2 DM***
(10% of all DM)	*(**80%-90%** of DM)*
*characterized by an **absolute** deficiency of insulin secretion caused by pancreatic β-cell destruction,.* * *	***("relative** insulin deficiency")*
*resulting from an **autoimmune attack***	*caused by a **combination** of (I) peripheral resistance to insulin action (II) an inadequate compensatory response of insulin secretion by the pancreatic β cells**("relative** insulin deficiency").* *Other causes make up the remaining DM cases*
● *All types of DM have the **same long-term complications** in kidneys, eyes, nerves, & BV & are the principal causes of morbidity & death.* * *	

Pathogenesis of Type 1 DM



F 20-21: Metabolic actions of insulin in striated muscle, adipose tissue, & liver.

Type 1 DM

is an ***autoimmune disease*

in which chronic destruction of islet β **cells is caused primarily by T lymphocytes reacting against, as yet, poorly defined β -cell

antigens (? Is the insulin hormone itself is the target antigen

for this autoimmune injury?) resulting in a reduction in β -cell mass (See F 20-22).

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Genetic susceptibility & **environmental** influences play important roles in the pathogenesis:

1-Type 1 DM has a ***complex pattern of genetic association****, the principal susceptibility locus for type 1 DM resides in the region that encodes the class II MHC molecules on chromosome 6p21 (HLA-D)*.

2- ***Environmental factors***, especially infections, may be involved in type 1 DM as in other autoimmune diseases.

☺ It has been **proposed that viruses may be an initiating trigger,** perhaps because some viral antigens are antigenically similar to β cell antigens **(molecular mimicry**), but this idea is **unproved.**

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☺The controversy is compounded by recent evidence indicating that **infections are actually protective**!!!

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Type 1 DM most commonly **develops in childhood, becomes **manifest at puberty** {the classic manifestations of DM of hyperglycemia & ketosis, occur late in its course, **after more than 90% of the β cells have been destroyed},** & is **progressive with age**.

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Type 1 DM diabetics depend on **exogenous insulin supplementation for survival, & without it, they develop serious complications such as acute ketoacidosis & coma.

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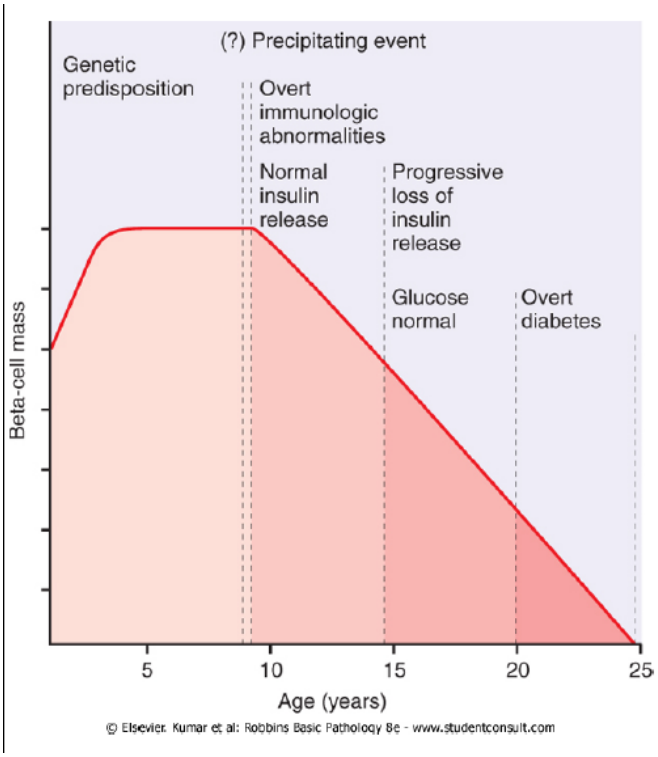

F 20-22: **Stages in the development of type 1 DM.**

The stages are listed from left to right, and hypothetical β-cell **mass** is plotted against **age.**

***Several mechanisms** contribute to β -cell destruction, & it is likely that many of these immune mechanisms work together to produce progressive loss of β cells,* resulting in DM

1) T lymphocytes **(CD4 + T cells of the TH1 subset)** react against β -cell antigens & cause cell damage, by activating:

(A) **Macrophages**

(B) **CD8+ cytotoxic T lymphocytes** which directly kill β cells & also secrete cytokines that activate macrophages.

In the early active stages of type 1 DM, the islets show cellular necrosis & lymphocytic infiltration *(insulitis).***

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2) Locally produced *cytokines* {including IFN-γ, produced by **T cells**, & TNF & IL-1 produced by activated macrophages} damage β cells.

3) ***Auto-Abs*** against a variety of β-cell antigens, including insulin & glutamic acid decarboxylase, are also detected in the blood of 70% to 80% of patients & may contribute to islet damage.

Pathogenesis of Type 2 DM

****remains mysterious!!!**

*****Genetic factors are even more important than in type 1 DM,* with linkage demonstrable to multiple "diabetogenic" Genes why ??

1) Among identical twins, the concordance rate is 50% to 90%

2)in **first-degree relatives** with type 2 DM (including fraternal twins) the risk of developing the disease is 20% to 40%, as compared with 5% to 7% in the population at large.

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Unlike type 1 DM, however, there is **no evidence to suggest an autoimmune basis to type 2 diabetes.

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***Two metabolic defects** :

(1) A primary ***insulin resistance, i.e.,*** *a ↓ ability of peripheral tissues to respond to insulin,* followed by increasing⋯.

(2) β -cell dysfunction, manifested as ***inadequate insulin secretion*** *in the face of insulin resistance & hyperglycemia* (F20-23).

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***Insulin Resistance**

1- Defined as: resistance to the effects of insulin on glucose uptake, metabolism, or storage.

2- Insulin resistance is a characteristic feature of most individuals with type 2 DM & is **universal finding in diabetic individuals who are obese.**

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The evidence that insulin resistance has a major role in the pathogenesis of type 2 DM come from two findings:

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(1) insulin resistance is often **detected 10 to 20 years before the onset of DM** in predisposed individuals (e.g., offspring of

type 2 diabetics), &

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(2) in **prospective studies**, insulin resistance is the **best predictor** for subsequent progression to DM.

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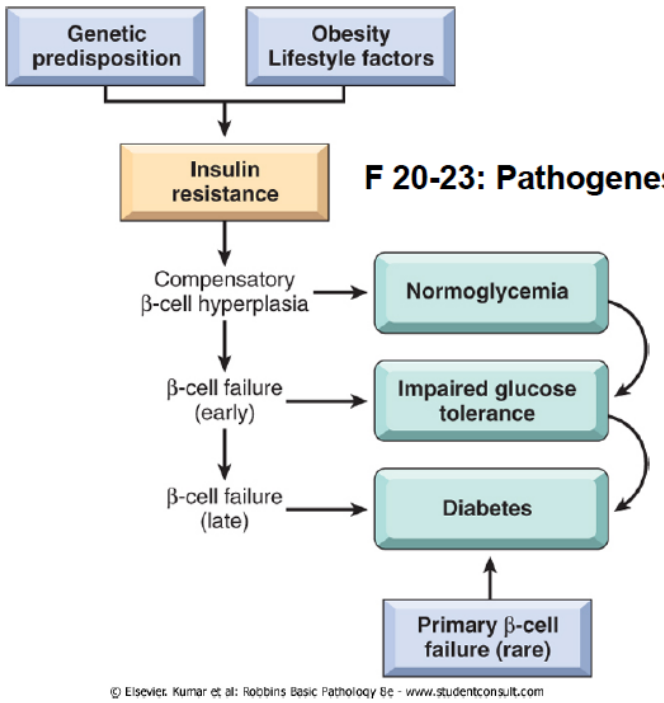

F 20-23: Pathogenesis of type 2 DM.

3- Insulin resistance is a complex multifactorial etiology phenomenon in humans, influenced by both genetic & environmental factors.

a) *Genetic Defects* *of the Insulin Receptor & Insulin Signaling Pathway* : are **not common**, & when present, they are more likely to be of mild effect.

b) *environmental factors* : *Obesity & Insulin Resistance:* With visceral obesity being common in the majority of type 2 diabetics, the association of obesity with type 2 DM has been recognized for decades.

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4-Insulin resistance is *the link between obesity & diabetes*

(F 20-24).

The risk for DM ↑ as the body mass index (a measure of body fat content) ↑, suggesting a dose-response relationship between body fat & insulin resistance.

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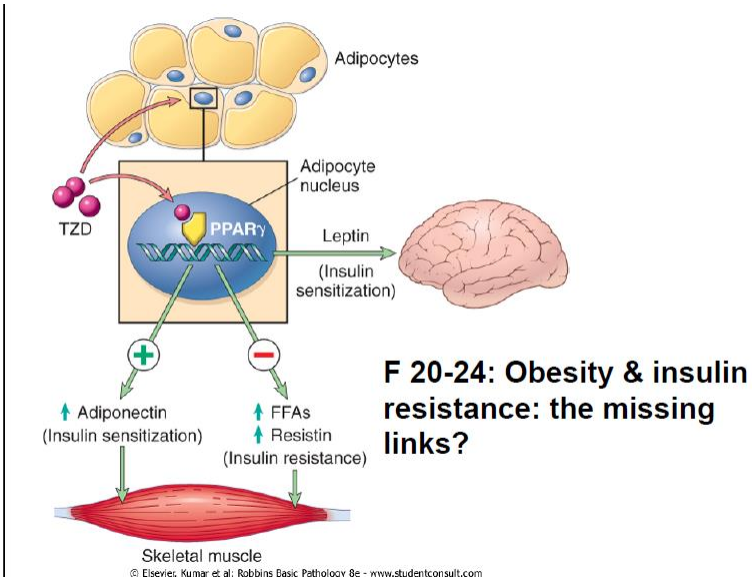
5- Possible pathways leading to insulin resistance:

a) ▲*Role of free fatty acids (FFAs):* Cross-sectional studies have demonstrated → an inverse correlation between fasting plasma FFAs & insulin sensitivity.



F 20-24: Obesity & insulin resistance: the missing links?

B) ▲ Role of adipocytokines in insulin resistance:

A dipocytokines;, *including (**& leptin, adiponectin** & **resistin)** are proteins produce by adipose tissue & are released into the systemic circulation;* changes in their levels are associated with insulin resistance; e.g.,:

****levels adiponectin** are *reduced* in states of obesity & insulin resistance, suggesting that, under physiologic conditions, this cytokine **contributes to insulin sensitivity** in peripheral tissues.

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****Conversely**, levels of **resistin** are ↑ in obesity, & this cytokine **contributes to insulin resistance**.

C) ▲Role of the PPAR & thiazolidinediones (TZD):

**TZDs, a class of anti-diabetic compounds, represent one of the major advances achieved in ↓ insulin resistance in DM.

The target receptor for TZDs has been identified as *PPAR*, a nuclear receptor & transcription factor. *PPAR is most highly expressed in adipose tissues, & its activation by TZDs results in modulation of gene expression in adipocytes,* **eventually leading to reduction of insulin resistance, & also ↓ concentrations of FFAs

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D) ▲A family of proteins called ***sirtuins,*** including **Sirt-1**, has been shown to **improve glucose tolerance, enhance β cell insulin secretion, & ↑ production of adiponectin.**

It remains to be seen if sirtuin abnormalities are involved in the pathogenesis of type 2 DM.

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β-Cell Dysfunction

** β -cell dysfunction in type 2 DM reflects the inability of these cells to adapt themselves to the long-term demands of peripheral insulin resistance & $\uparrow$ insulin secretion.

▲ **In states of insulin resistance, insulin secretion is initially higher for each level of glucose than in controls. This hyperinsulinemic state is a compensation for peripheral resistance & often maintain normal plasma glucose for years!

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▼ **Eventually, however, β -cell compensation becomes inadequate, & there is progression to overt DM.

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The underlying **bases for failure of β -cell adaptation is not known. It is postulated that several mechanisms, including:

1- adverse effects of high circulating FFAs ("lipotoxicity")

2- or chronic hyperglycemia ("glucotoxicity"),

may have a role.

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** β *-cell dysfunction in type 2 DM encompasses both qualitative & quantitative aspects.*

a) ▼**Qualitative β -cell dysfunction** is

-initially manifest as loss in the subtle abnormalities, such as

(1) normal pulsatile,oscillating pattern of insulin secretion, &

(2) attenuation of the rapid first phase of insulin secretion triggered by elevation in plasma glucose.

- Over time, the secretory defect progresses to encompass all phases of insulin secretion, & even though some basal insulin secretion persists in type 2 DM, it is **inadequate** for overcoming insulin resistance.

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b) ▼**Quantitative β -cell dysfunction is manifest as a**

1. ***↓ in β -cell mass,***

2.islet degeneration

3. deposition of islet amyloid.

Islet amyloid protein (amylin) is a characteristic finding in individuals with type 2 DM, & it is present in more than 90% of diabetic islets examined.

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-Islet amyloidosis is associated with a $\downarrow$ in β -cell mass,

although it is uncertain, **whether the amyloid is a cause or consequence of cell damage in type 2 DM?**

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-Even a "normal" β -cell mass in diabetic individuals may, in fact, indicate a relative reduction as compared with the expected hyperplasia needed to compensate for insulin resistance.

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Monogenic Forms of Diabetes

Types 1 & 2 DM are genetically complex, & despite the associations with multiple susceptibility loci, no single gene defect (mutation) can account for predisposition to these entities.

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In contrast, monogenic forms of diabetes (Table 20-5) are uncommon examples of the *diabetic phenotype occurring secondary to loss-of-function mutations within a single gene.* Monogenic causes of DM result from either a primary defect in β -cell function or a defect in insulin-insulin receptor signaling.

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Pathogenesis of the Complications of Diabetes

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-The diabetic complications are a consequence of **hyperglycemia** .

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-Three distinct metabolic pathways seem to be involved in the pathogenesis of long-term diabetic complications, the **primacy** of any one has not been established. These 3 pathways include:

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1. ***Non-enzymatic glycosylation***.

-This is the process by which **glucose chemically attaches to free amino groups of proteins without the aid of enzymes.**

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-Its degree is directly related to blood glucose level; indeed, the **measurement of glycosylated Hb (Hb A1C) levels in blood (Normal level <6 units) is useful in the management of DM,** as it provides an **index** of the **average blood glucose levels over the 120-day life span of RBCs,**

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-The **early glycosylation** products of collagen & other longlived proteins in interstitial tissues & BV walls undergo a slow series of chemical rearrangements to form ***irreversible advanced glycosylation end products*** **(AGEs),** which accumulate over the lifetime of the BV wall.

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-**AGEs** have a number of chemical & biologic properties that are pathogenic to ECM components & to the target cells of diabetic complications:

****AGEs** formation on proteins such as collagen causes crosslinks between polypeptides; this in turn may **trap** nonglycosylated plasma & interstitial proteins.

(I) In **large BV,** trapping **LDL**, for example, retards its efflux from the BV wall & **enhances** the deposition of cholesterol in the intima, thus accelerating **atherosclerosis.**

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(II) In **capillaries**, including **renal glomeruli**, plasma proteins such as **albumin bind to the glycated BM,** accounting in part for the **diffuse glomerular capillary BMs** thickening, throughout their entire length characteristic of diabetic glomerulopathy.

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(III) **Circulating plasma proteins are modified by the addition of AGE residues;** these proteins, in turn, **bind to AGE receptors** on several cell types (ECs, mesangial cells, & macrophages).

The biologic effects of **AGE-receptor signaling** include the following

(1) release of cytokines & GFs from macrophages & mesangial cells;

(2) ↑ endothelial permeability;

(3) ↑ procoagulant activity on ECs & macrophages; &

(4) enhanced proliferation & synthesis of ECM by fibroblasts & SMCs.

All these effects can potentially contribute to diabetic complications.

2. ***Activation of protein kinase C*** **(PKC**).

Intracellular hyperglycemia can stimulate the de novo the second messenger synthesis of diacylglycerol (DAG), causes activation of intracellular protein kinase C (PKC).

The down-stream effects of PKC activation are:

(A) Production of *pro-angiogenic molecules* such as VEGF implicated in the **neovascularization** seen in **diabetic retinopathy**, &

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(B) pro-fibrogenic molecules like (TGF- β), leading to ↑ deposition of ECM & BM material

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3. ***Intracellular hyperglycemia*** *disturbances in polyol pathways.* In some tissues that do not require insulin for glucose transport (e.g., **nerves, lens, kidneys,& BV**), hyperglycemia leads to an ↑ in intracellular glucose that is then metabolized by the enzyme *aldose reductase* to sorbitol, a polyol, & eventually to fructose.

Accumulated sorbitol & fructose cause cell injury via;

(A) ↑ **intracellular osmolarity & water influx**,

(B) **An ↑ in cellular susceptibility to oxidative stress.**

Morphology of DM & Its Late Complications

**There is extreme variability among patients in

-the time of onset of diabetic complications

- their severity, &

-the particular organ or organs involved.

**In individuals with tight control of DM the onset may be delayed.

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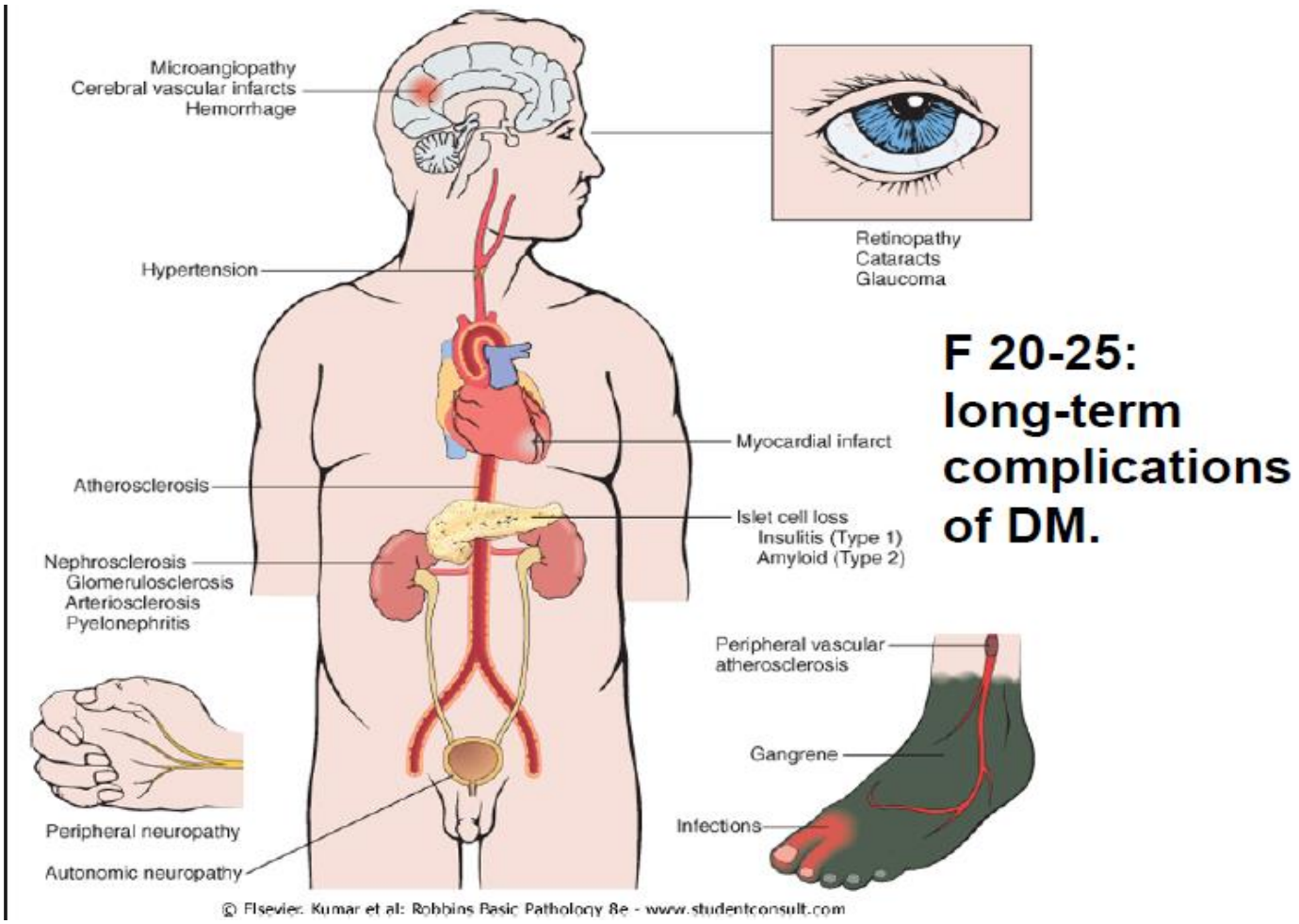
**In most patients, however, morphologic changes are likely to be found in

-arteries **(macrovascular disease)**

- BMs of small BV **(microangiopathy)**

- kidneys **(nephropathy),** retina **(retinopathy),** nerves **(neuropathy),** & other tissues.

**These changes are seen in both type 1 & 2 DM (F 20-25



F 20-25: long-term complications of DM.

Pancreas in DM

**Lesions in the pancreas are inconstant & rarely of diagnostic value.

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**Distinctive changes are more commonly associated with type 1 than with type 2 DM.

**One or more of the following alterations may be present:

1-▼ Reduction in the number & size of islets: most often seen in type 1 DM, most of the islets are small & inconspicuous,

2- ▼ Insulitis, with WBC infiltration of the islets, principally composed of T lymphocytes (F20-26A).

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3-► **In type 2 DM there may be a mild reduction in islet cell mass,** demonstrated only by special morphometric studies.

4-► **Amyloid replacement of islets in long-standing type 2 DM** appears as deposition of pink, amorphous material beginning in & around capillaries & between cells.

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-At advanced stages the islets may be virtually obliterated (F20-26B); fibrosis may also be observed.

This change is often seen in long-standing cases of type 2 DM.

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N.B;-Similar lesions may be found in elderly nondiabetics, apparently as part of normal aging.

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نوتس الصور :

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****An ↑ in the number & size of islets** is especially characteristic **of nondiabetic newborns of diabetic mothers.** Presumably, fetal islets undergo hyperplasia in response to the maternal hyperglycemia.

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Diabetic Macrovascular Disease

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(A) The hallmark of which is **accelerated atherosclerosis**, with greater severity & earlier age of onset.

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(1) MI caused by atherosclerosis of the coronary arteries, is the most common cause of death in both diabetic women & men, whom are affected equally.

In contrast, MI is uncommon in nondiabetic women of reproductive age.

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(2) Gangrene of the lower extremities, resulting from advanced vascular disease, is **100 times more common in diabetics** than in the general population.

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(3) In DM, the **larger renal arteries (which rarely affected by atherosclerosis) are subject to severe atherosclerosis**.

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(B) Hyaline arteriolosclerosis,

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the vascular lesion associated with **hypertension (Which type? Benign)

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is both more prevalent & more severe in **diabetics than in nondiabetics,"

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****but it is not specific** for diabetes & may be seen in **elderly** nondiabetics without hypertension.

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It takes the form of an amorphous, hyaline thickening of the wall of the arterioles,which causes **narrowing of the lumen (F20-27).

Diabetic Microangiopathy

One of the most consistent morphologic features of DM is **diffuse thickening of BMs.

The thickening is most evident in the **capillaries of the **retina, renal glomeruli** & medulla,skin and skeletal muscle, .

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**However, it may also be seen in such nonvascular structures as renal tubules, Bowman capsule, peripheral nerves, & placenta.

By both light & EM, the **BMs are markedly thickened by concentric layers of hyaline material composed mainly of **type IV collagen** (F20-28).

نوتس على الصورة 27-20 :

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نوتس على صورة 28-20 :

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It should be noted that **the thickness of BMs, diabetic capillaries are more leaky than normal to plasma proteins.

The microangiopathy underlies & and causes the development of diabetic **nephropathy,**retinopathy, & some forms of neuropathy.**

NB. "**As in *hyaline arteriolosclerosis***, the ***microangiopathy*** is ***not specific change*** & can be found in **aged nondiabetic** patients, but rarely to the extent seen in individuals with longstanding DM" .

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Diabetic Nephropathy:

The kidneys are prime targets of DM. **Renal failure is 2nd** only to **MI** as a cause of death from DM, renal 3 lesions are:

(I) **Glomerular** lesions;

(II) **Renal atherosclerosis** & arteriolosclerosis; &

(III) **Pyelonephritis**, including necrotizing papillitis.

(I) The most important **glomerular lesions** are

▼ **Diffuse** capillary BM thickening (F 20-29),

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▼ **Diffuse** mesangial sclerosis, &

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▼ **Nodular** glomerulosclerosis (***Kimmelstiel-Wilson*** (F20-30).

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▼**There is diffuse glomerular capillary BMs** thickening, throughout their entire length (F20-29).

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▼**Diffuse mesangial sclerosis** consists of a diffuse ↑ mesangial matrix along with mesangial cell proliferation & is **always associated with BM thickening**.

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**It is found in most individuals with DM of more than 10 years' duration.

When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, & edema.

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Diffuse mesangial sclerosis is **not specific, as it may also be seen in association with old age & hypertension

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▼Nodular glomerulosclerosis

is distinctive **ball-like deposits of a laminated matrix situated in the periphery of the glomerulus (F20-30).

**These nodules are PAS positive & usually contain trapped mesangial cells.

This **pathogonomic (specific) change has been called the **Kimmelstiel-Wilson lesion**, after the pathologists who described it.

**Nodular glomerulosclerosis is encountered in approximately 15% to 30% of long-term diabetics & is a major cause of morbidity & mortality.

نوتس الصورة 20-29 :

نوتس على الصورة 20-30 :

Both the diffuse & the nodular forms of glomerulosclerosis induce sufficient **ischemia to cause scarring of the kidneys, manifested by a finely granular cortical surface (F20-31).

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(II) **Renal atherosclerosis & hyaline arteriolosclerosis constitute part of the macrovascular disease in DM.**

**The kidney is one of the most frequently & severely affected organs.

****Hyaline arteriolosclerosis affects not only the afferent but also the efferent arterioles.**

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Such efferent arteriolosclerosis is **rarely if ever, encountered in persons who do not have DM!

(III) **Acute or chronic pyelonephritis,** usually begins in the renal interstitial tissue & then spreads to affect the tubules. Both occur more commonly & more severely in diabetics than in the non-diabetics.

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A special, more dangerous pattern of acute pyelonephritis called **necrotizing papillitis** (or **papillary necrosis**), is much more prevalent in diabetics than in nondiabetics.

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نوتس الصورة 31-20 :

Ocular Complications of Diabetes

**Diabetic ocular involvement may take the form of

1-**retinopathy,**

2-cataract,

3- or glaucoma,

causes visual impairment, up to total blindness, is one of the most feared consequences of long- standing DM .

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Retinopathy takes two forms:

(1) nonproliferative (background) retinopaty &

(2) proliferative retinopathy.

▼▼**Nonproliferative retinopathy** includes, most importantly, thickening of the retinal capillaries (micro-angiopathy).

1-intra-retinal or pre-retinal hemorrhages,

2- retinal exudates,

3-microaneurysms,

4- venous dilations & edema.

****Retinal exudates** can be either "soft" (microinfarcts) or "hard" (deposits of plasma proteins & lipids) (F20-32).

****Microaneurysms** are discrete saccular dilations of retinal choroidal capillaries that appear through ophthalmoscope as small red dots.

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excessive capillary permeability causes retinal **edema.

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****Underlying all these changes is the microangiopathy**, which is thought to lead to loss of capillary pericytes & hence to focal weakening of capillary structure

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صورة 20-32 :

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▼▼**Proliferative retinopathy** is neovascularization (formation of new BVs and capillaries) & fibrosis.

****Rupture** of newly formed capillaries cause → vitreous hemorrhages, → **organization** of the hemorrhage can pull the retina off its substratum, i.e., **retinal detachment.** leading to serious consequences, including **blindness**, especially if it involves the macula.

* vitreous :

*substratum

***retinal detachment**

*** macula**

Diabetic Neuropathy

The most frequent pattern of involvement of the peripheral & CN systems are (1) **a peripheral symmetric neuropathy of the lower extremities that affects both motor & sensory function but particularly the latter,

(2) **peripheral neuropathy**, which produces disturbances in bowel & bladder function, sometimes **sexual impotence**, &

(3) **diabetic mononeuropathy**, which may manifest as sudden **footdrop, wristdrop**, or isolated cranial nerve palsies.

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The neurologic changes may be **caused by** :

(1) microangiopathy & ↑ permeability of the capillaries that supply the nerves, &

(2) direct axonal damage due to alterations in sorbitol metabolism.

***Clinically**, presentations of DM are divers. (Table 20-6).

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1) → **Hyperglycemia,** exceeds the renal threshold for glucose reabsorption leads to → **glycosuria,** which induces an osmotic diuresis & → ***polyuria,*** **causing a profound,** obligatory **loss of water & electrolytes**.

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The renal water loss, combined with the hyperosmolarity resulting from hyperglycemia → **deplete intracellular water, triggering the osmoreceptors of the → **thirst centers of the brain**.

This intense **thirst → leads to *(polydipsia= excessive water intake).***

السيناريو :

2) → **Catabolism of proteins & fats** tends to induce a negative energy balance, which in turn leads to ↑ appetite → ***polyphagia,***

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thus completing the **classic triad of diabetes**: {***polyuria + polydipsia + polyphagia***}.

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Despite the ↑ appetite, catabolic effects prevail, resulting in → **weight loss & **muscle weakness**.

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The combination of polyphagia & weight loss is **paradoxical & should always raise the suspicion of DM.

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PANCREATIC ENDOCRINE NEOPLASMS

●***Pancreatic endocrine neoplasms,*** or **"islet cell tumors,"** are **Rare,** in comparison with tumors of the exocrine pancreas (80%),accounting for 2% of all pancreatic neoplasms only.

● Most common in **adults,** may be **single or multiple**, May be **benign, or malignant** metastasizing to LNs & liver.

● Many are **functional,** elaborating pancreatic hormones, but some are **nonfunctional.**

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●Like any other endocrine neoplasms, it is difficult to predict the biologic behavior of a pancreatic endocrine neoplasm purely on the basis of **light microscopic criteria**.

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►**Generally**, **tumors less than 2 cm in size,** tend to behave in an indolent (very slowly growing) manner (but there are significant exceptions).

► **90% of insulinomas** (the most common subtype of pancreatic endocrine neoplasms)	**other**
are benign	►while up to **90% of other** functioning & nonfunctioning pancreatic endocrine neoplasms tend to be malignant

Insulinomas (β -cell tumors)

of pancreatic Are the **most common** endocrine neoplasms, resulting in a characteristic clinical triad of:

(1) **Attacks of hypoglycemia,** occur with blood serum glucose levels below 50 mg/dL;

(2) **Attacks** consist principally of CNS manifestations as confusion, stupor, & loss of consciousness; &

(3) The **attacks are precipitated by fasting or exercise** & are promptly (rapidly) **relieved** by feeding or parenteral administration of glucose

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Morphology of insulinomas (F 8.26)

 # grossly :

Most are found **within the pancreas & **90%** are **benign**.

Most are **solitary lesions although multiple tumors or tumors ectopic to the pancreas may be encountered.

Solitary tumors are usually **small (often <2 cm in Ø) & are **Encapsulated**, pale to red-brown nodules within pancreas.

Bona fide **carcinomas making up only about **10%** of cases, , are diagnosed on the basis of **metastases.**

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#◙ H,

****benign** insulinomas **look remarkably like giant islets,** with preservation of the regular cords of monotonous cells & their orientation to the vasculature (F20-34A).

****Insulin can be localized in the tumor cells** by immunocytochemistry (F20-34B).

Even the **malignant insulinomas may not present much evidence of anaplasia & some may be deceptively encapsulated!!!

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While as many as 80% of insulinomas may show excessive insulin secretion, **hypoglycemia is mild in all, but 20%.

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The critical laboratory findings in insulinomas are **high** circulating levels of **insulin** & a high insulin-to-glucose ratio.

Surgical removal of the tumor is **curative.**

Remember: Besides insulinomas, there are many other causes of ***hypoglycemia,* including

(1) *self-injection* of insulin,

(2) *diffuse liver disease*, &

(3) secretion of insulin-like growth factor-2 (IGF-2) by some *fibrosarcomas*

نوتس على الصورة 20-34 :

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Gastrinomas

● Gastrinomas, with marked hypersecretion of gastrin may arise in the pancreas, peripancreatic region, or the wall of the duodenum (so-called **"gastrinoma triangle").**

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● **Over 50% of gastrin-producing tumors** are locally invasive or have already **metastasized** at the time of diagnosis.

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● In approximately **25% of patients**, gastrinomas (frequently **multifocal**) arise in conjunction with other endocrine tumors, thus conforming to the **MEN-1 syndrome**.

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● **Sporadic** gastrinomas are usually **single.** As with insulin-secreting tumors of the pancreas, gastrin producing tumors are histologically bland & rarely exhibit marked anaplasia.

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●**Zollinger & Ellison** first called attention to the associatio*n of 1- pancreatic islet cell lesions with 2- hypersecretion of gastric acid & 3- severe peptic ulceration,* which are present in up to 95% of patients (Zollinger-Ellison syndrome), in which

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► **Hypergastrinemia** from a pancreatic or duodenal tumor stimulates extreme gastric acid secretion, which causes

► ***Peptic ulceration****.* The duodenal & gastric ulcers are often to usual modalities of therapy; ulcers

►***intractable*** & ***Multiple*** may also occur in

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► ***Unusual locations*** **such as the jejunum,** (when intractable jejunal ulcers are found, Zollinger-Ellison syndrome should

be considered),

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►More than 50% of the patients have **diarrhea in 30%;**

it is the presenting symptom.

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Other Rare Pancreatic Endocrine Neoplasms

● α ***-Cell tumors (glucagonomas)*** are associated with

** ↑ serum glucagon & a syndrome consisting of **mild diabetes mellitus,**

****a** characteristic **skin rash** *(necrolytic migratory erythema),* & ****anemia.**

They occur most frequently in peri- & postmenopausal women & are **characterized by extremely high plasma glucagon levels**.

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● δ *-Cell tumors (**somatostatinomas)*** are associated with DM, cholelithiasis, steatorrhea, & hypochlorhydria. They are exceedingly difficult to localize preoperatively.

☼ **High plasma somatostatin levels are diagnostic**.

● ***VIPoma*** = **Vasoactive Intestinal peptide (VIP) producing tumor** is an endocrine T that induces the characteristic syndrome *(watery diarrhea, hypokalemia, achlorhydria, socalled WDHA syndrome)*, caused **by release of** vasoactive intestinal peptide **(VIP)** from the T.

Some of these T are locally invasive & metastatic.