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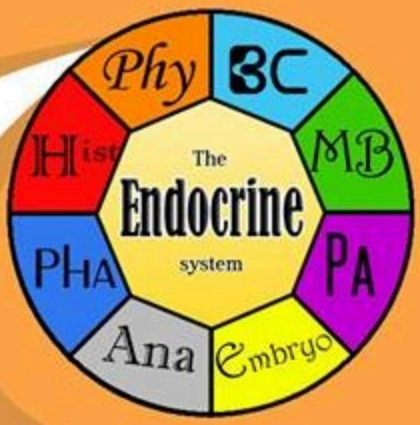
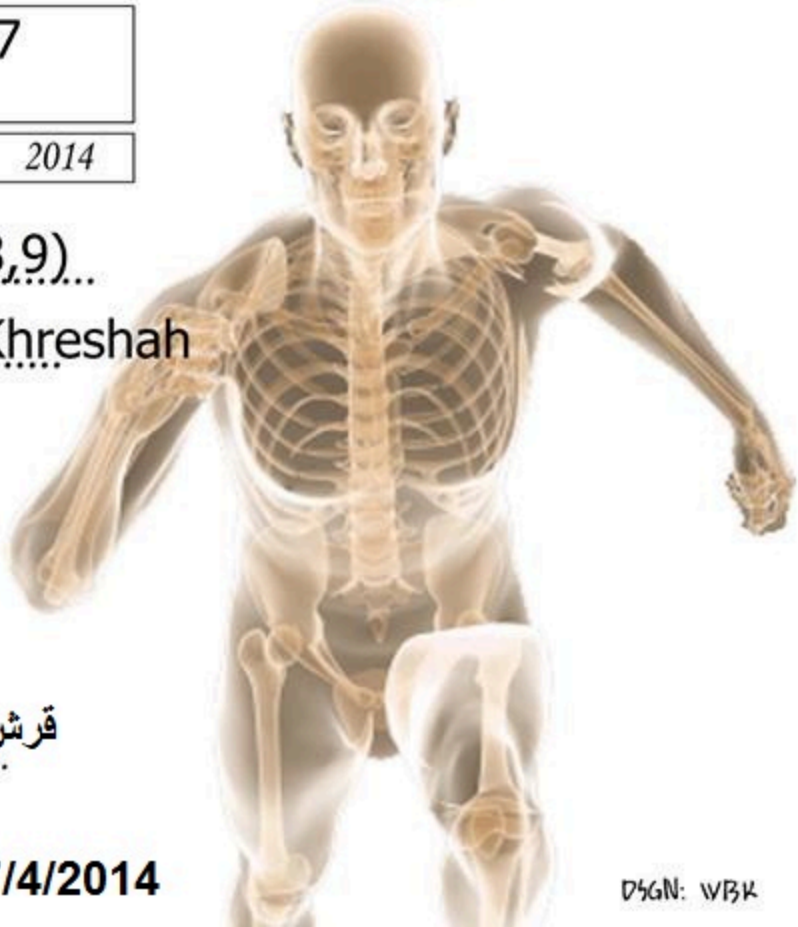



# Physiology

■ Slides #7
□ Sheet
2014



Title: Pancreas (lct. 8,9)

Professor: Dr.Saleem Khreshah

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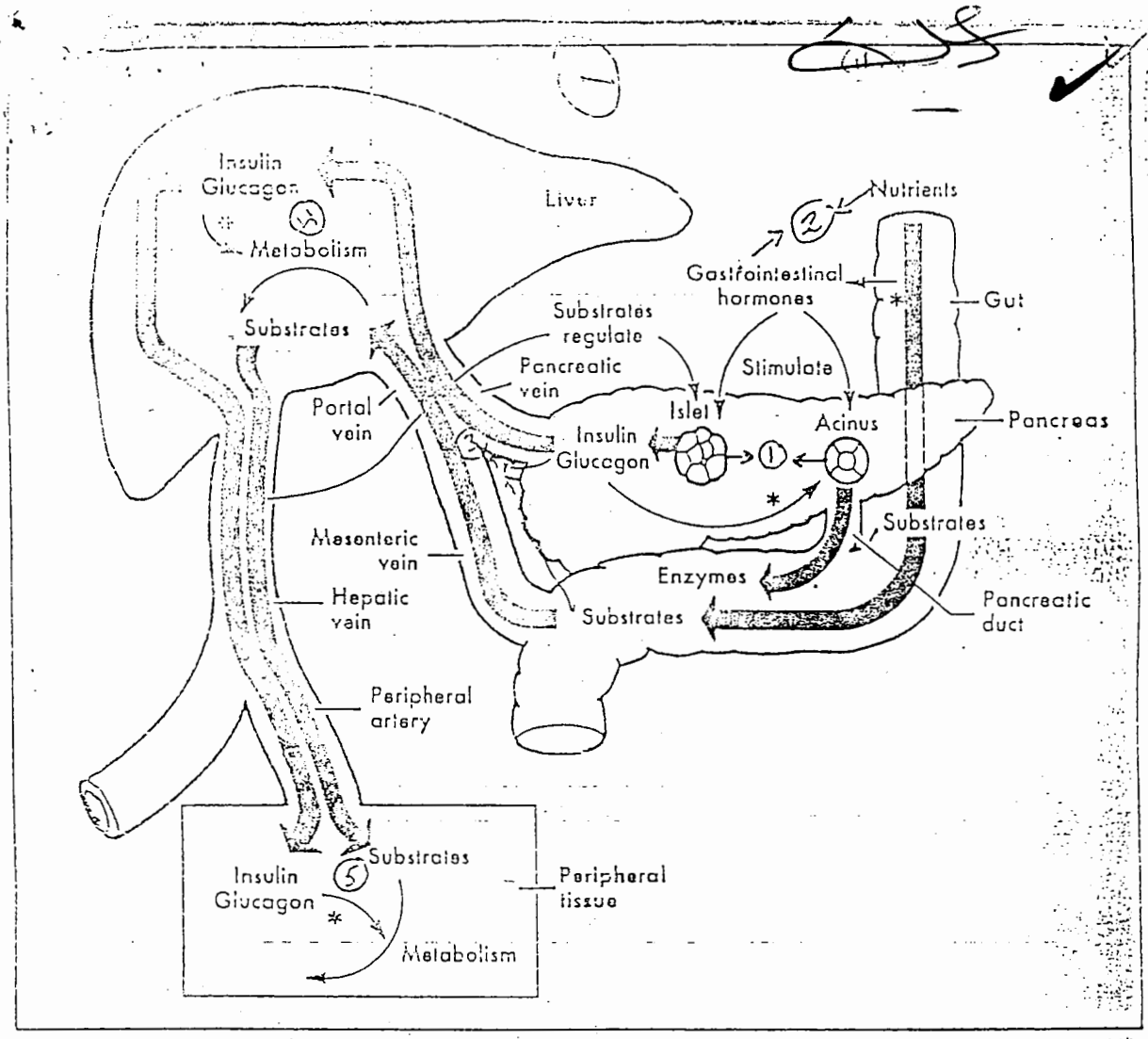



FIGURE 37-1 A schematic view of the pivotal location of the pancreatic islets. Secretion of the islet hormones insulin and glucagon is coordinated with secretion of exocrine pancreatic enzymes. Both are stimulated by entry of nutrients into the gastrointestinal tract and by gastrointestinal hormones. Islet hormones are secreted into the portal vein and thereby reach the liver with the substrate products of nutrient digestion. Within the liver they affect the metabolism of the ingested substrates. Islet hormones that pass through the liver with substrates affect disposition of these substrates by peripheral tissues. In turn these substrates feed back on the pancreatic islets to modulate the secretion of insulin and glucagon.

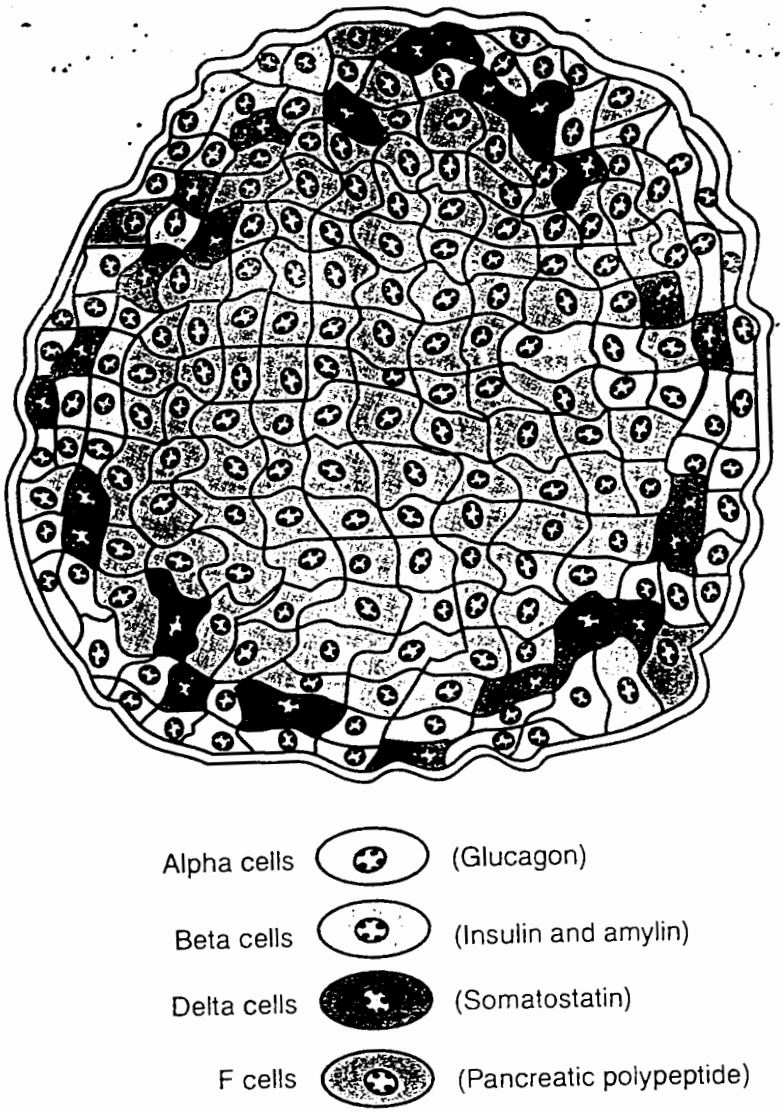


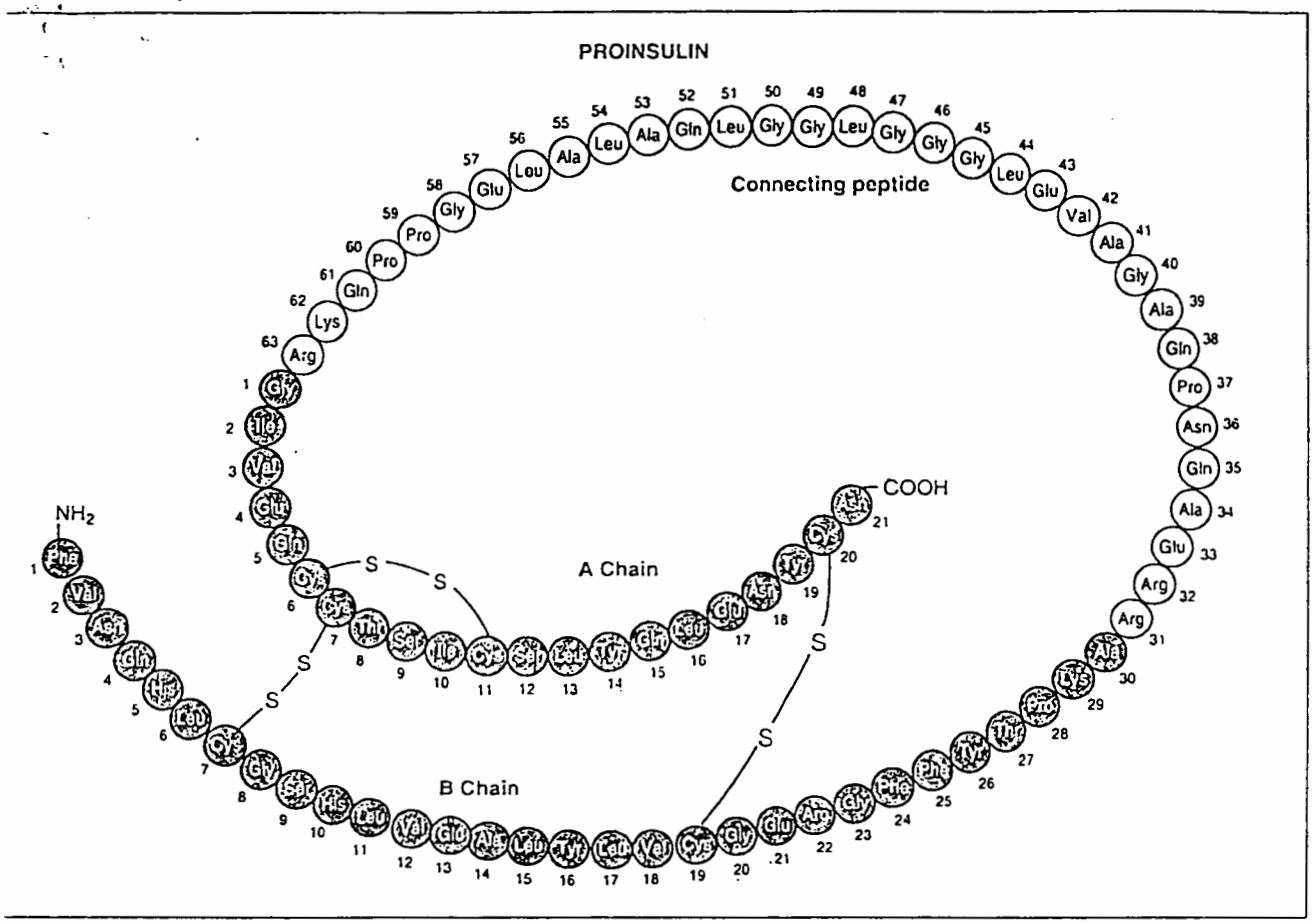

**FIGURE 34.1 Major cell types in a typical islet of Langerhans.** Note the distinct anatomic arrangement of the various cell types. (Modified from Orci L, Unger RH. Functional subdivision of islets of Langerhans and possible role of D cells. Lancet 1975;2:1243–1244.)

Amylin is a 37–amino acid peptide that is almost exclusively expressed within pancreatic beta cells, where it is copackaged with insulin in secretory granules. Preclinical data indicate that amylin acts as a neuroendocrine hormone that complements the actions of insulin in postprandial glucose homeostasis via several mechanisms. These include a suppression of postprandial glucagon secretion and a slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption.

Table 19–1. Cell types in pancreatic islets of Langerhans.

| Cell Types | Approximate % of Islet Mass | Secretory Products |
|---|---|---|
| A cell ($\alpha$) | 20% | Glucagon, proglucagon |
| B cell ($\beta$) | 75% | Insulin, C peptide, proinsulin |
| D cell ($\delta$) | 3–5% | Somatostatin |
| F cell (PP cell) | < 2% | Pancreatic polypeptide |

Pancreatic islets of Langerhans comprise 1% to 2% of the mass of pancreas and are scatered through out the organ




URE 9–26. Structure of porcine proinsulin. The connecting peptide (C peptide) is cleaved to form insulin. (Modified with mission from W. N. Shaw and R. R. Chance. Effect of porcine proinsulin in vitro on adipose tissue and diaphragm of the normal rat. betes 17:737, 1968.)

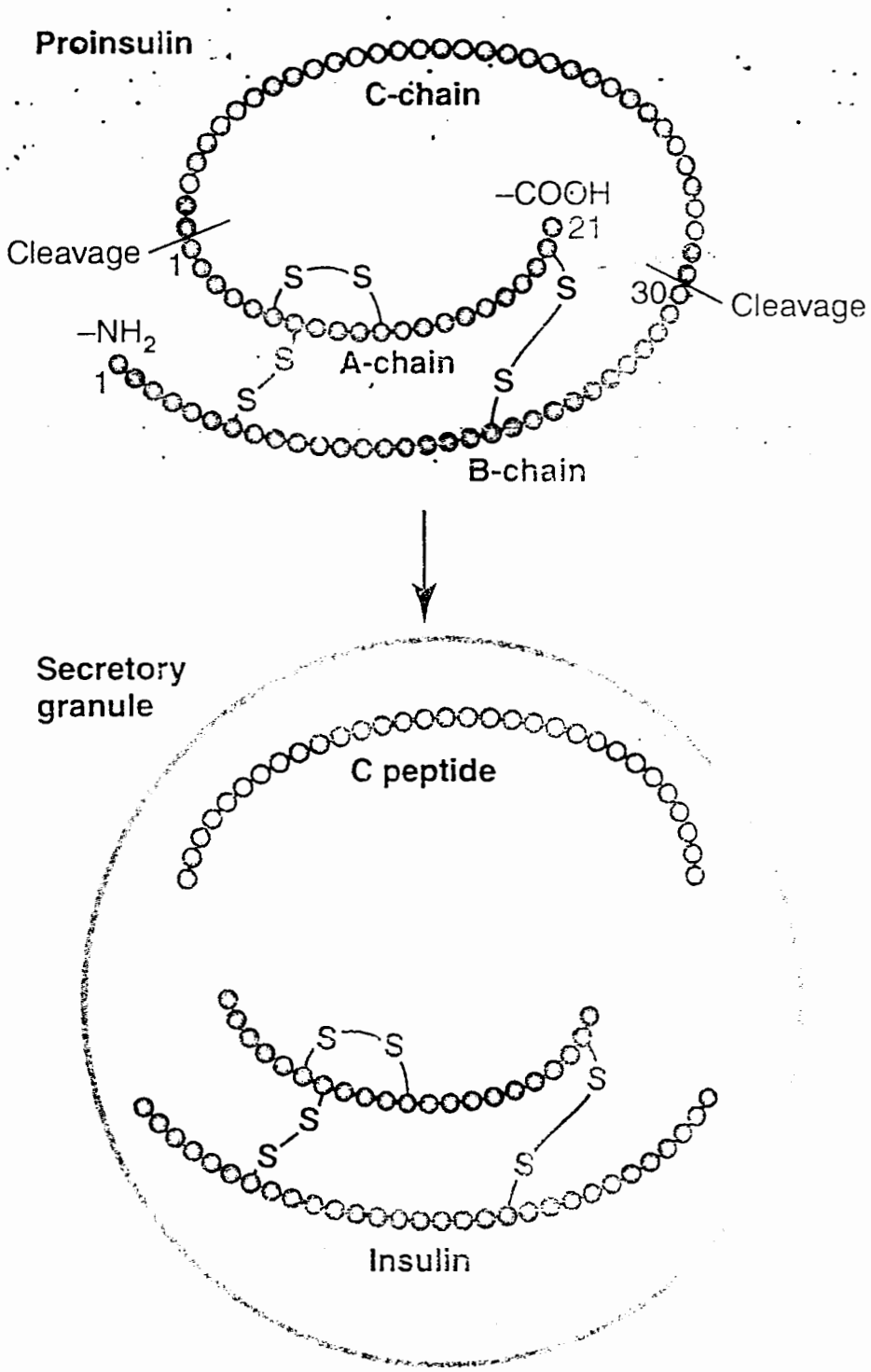



**Figure 78-2** Schematic of the human proinsulin molecule, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin, which is composed of the A and B chains connected by disulfide bonds. The C peptide and insulin are packaged in granules and secreted in equimolar amounts, along with a small amount of proinsulin.

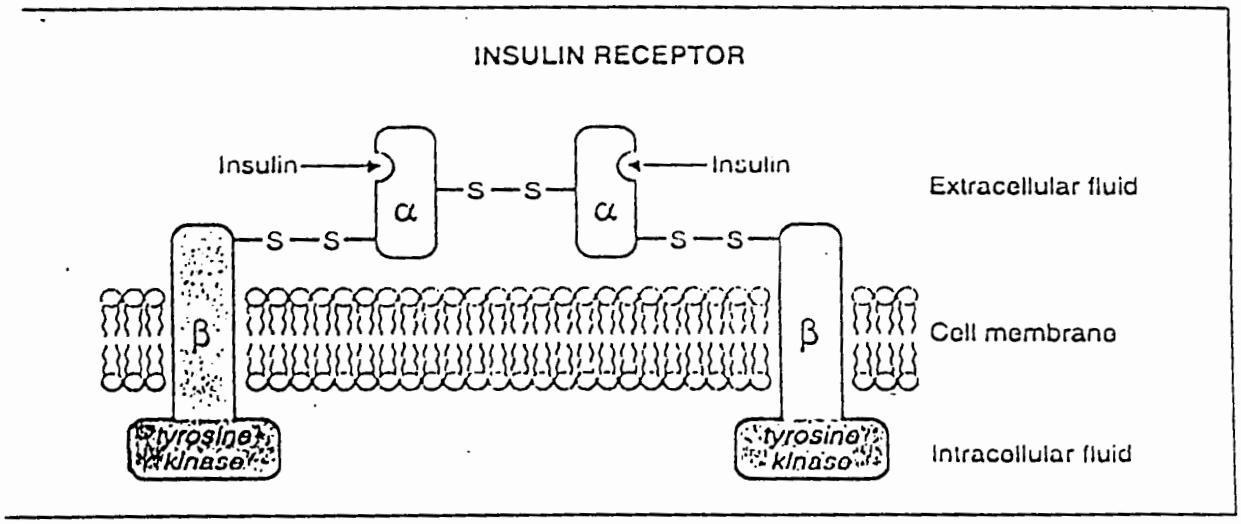



FIGURE 9–28. Structure of the insulin receptor. The two α subunits are connected by disulfide bonds; each α subunit is connected to a β subunit by a disulfide bond. The β subunits have tyrosine kinase activity.

Insulin receptors are found on many different cells in the body, including cells in which insulin does not increase glucose uptake. The receptor is made up of 2 α and 2 β glycoprotein subunits. The subunits are linked to each other and to β subunits by disulfide bonds. The α subunits bind insulin and are extracellular, whereas the β subunits span the membrane. The intracellular ends of the β subunits have tyrosine kinase activity. Binding of insulin triggers the tyrosine kinase activity of the β subunits, producing autophoisphorylation of the β subunits on tyrosine residues. This autophosphorylation in necessary for insulin to exert its biologic effects.

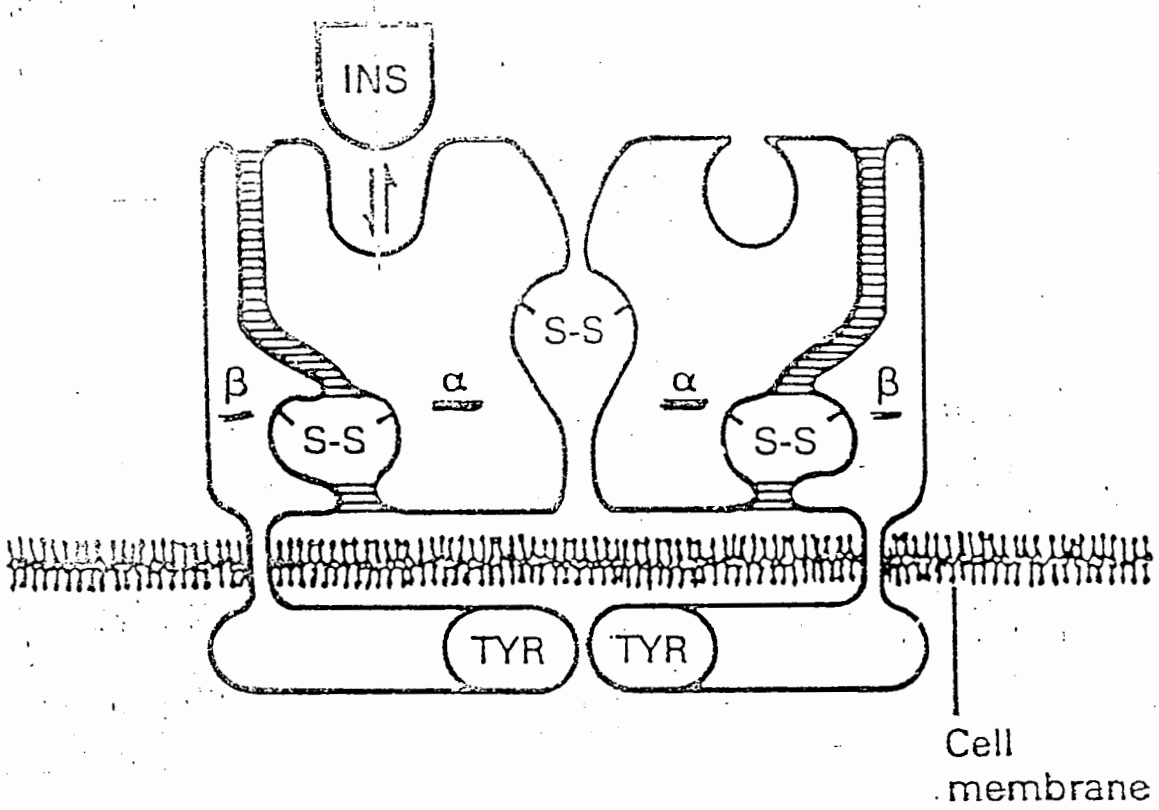



**Figure 19-5.** Diagrammatic representation of the structure of the insulin receptor. The receptor is a tetrameric protein made up of 2 $\alpha$ and 2 $\beta$ subunits joined by disulfide (—S—S—) bonds. Insulin (INS) binds to the $\alpha$ subunits and this triggers autophosphorylation of the tyrosine kinase portions of the $\beta$ subunits inside the cell. The autophosphorylation in turn triggers the rest of the multiple and extensive effects of insulin (Modified from Andersen AS: Reception and transmission *Nature* 1989;**337:**12.)

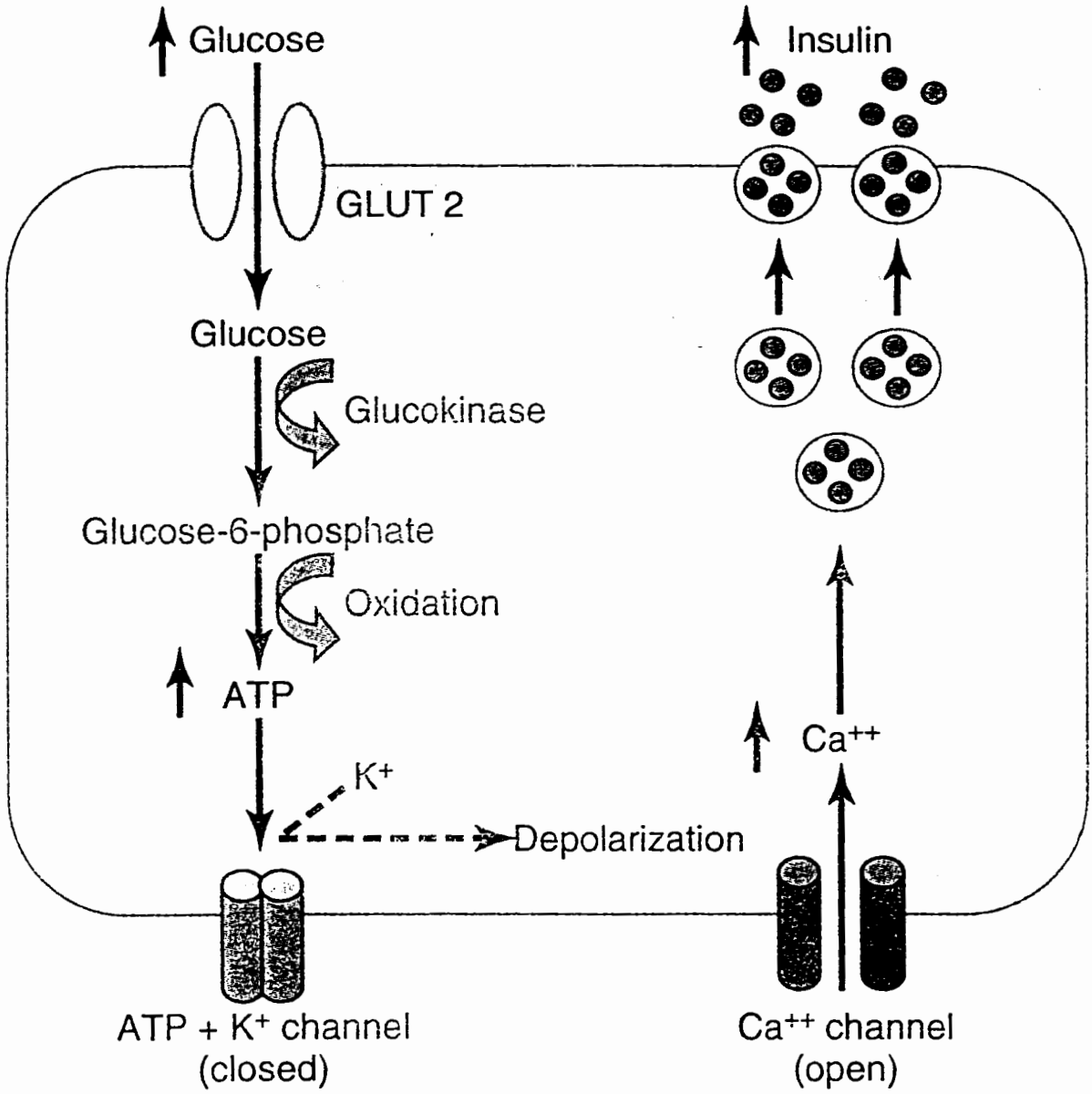



**Figure 78-7** Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

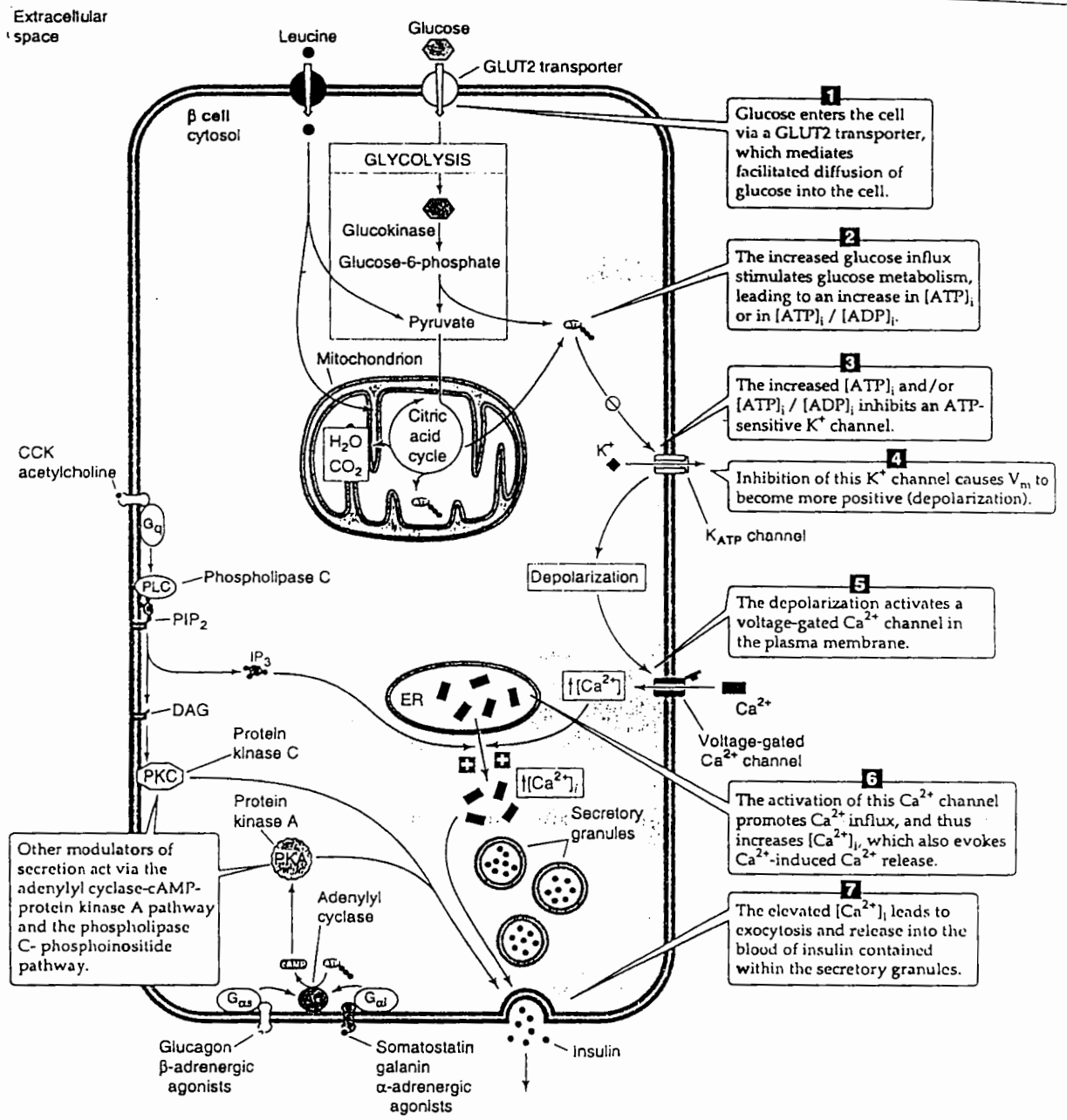



FIGURE 50–4. Mechanism of insulin secretion by the pancreatic $\beta$ cell. Increased levels of extracellular glucose trigger the $\beta$ cell to secrete insulin in the seven steps outlined in this figure. Metabolizable sugars (e.g., galactose and mannose) and certain amino acids (e.g., arginine and leucine) can also stimulate the fusion of vesicles that contain previously synthesized insulin. In addition to these fuel sources, certain hormones (e.g., glucagon, somatostatin, CCK) can also modulate insulin secretion. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CCK, cholecystokinin; DAG, diacylglycerol; ER, endoplasmic reticulum; $IP_3$, inositol 1,4,5-triphosphate; $PIP_2$, phosphatidylinositol 4,5-biphosphate; PKA, protein kinase A; PLC, phospholipase C.

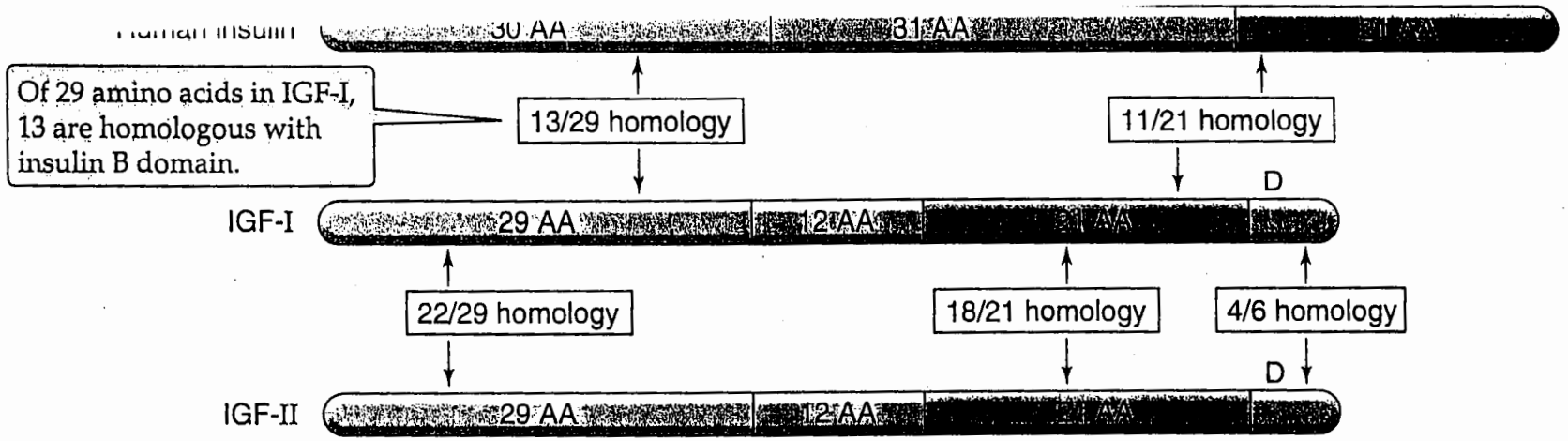



FIGURE 47–5. Structure of the insulin-like growth factors (IGFs). Insulin, IGF-I, and IGF-II share three domains (A, B, and C), which share a hig degree of amino acid sequence homology. The C region is cleaved from insulin (as the C peptide) during processing, but is not cleaved from eithe IGF-I or IGF-II. In addition, IGF-I and IGF-II also have a short D domain.

## Insulin-Like Growth Factor I, Which Interacts with a Receptor Similar to the Insulin Receptor, Is the Principal Mediator of the Growth-Promoting Action of Growth Hormone

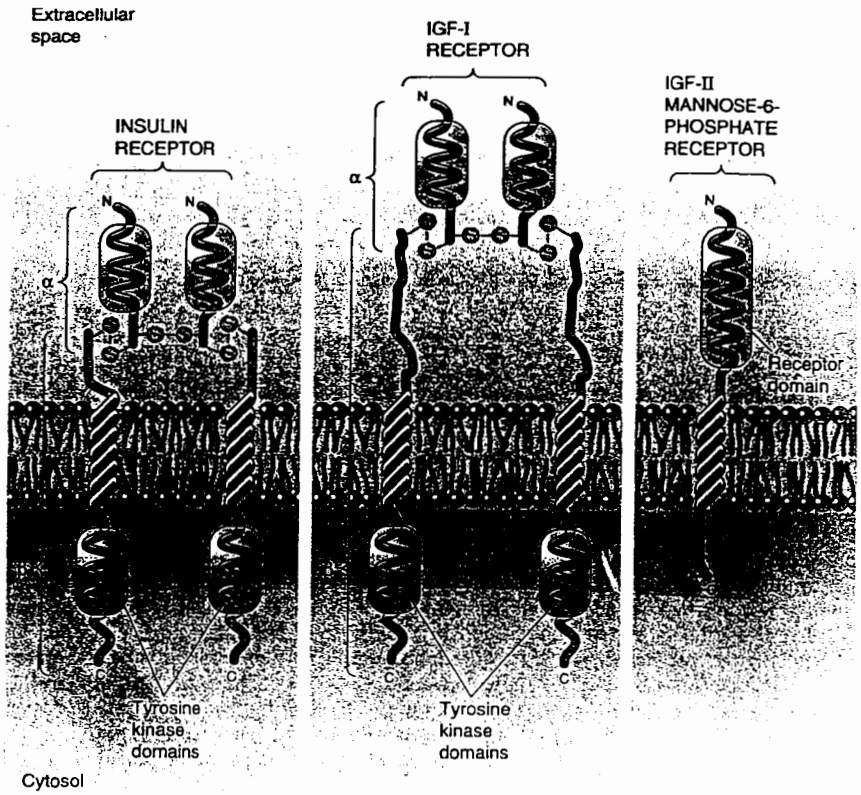



FIGURE 47–6. Comparison of insulin, insulin-like growth factor (IGF)-I, and IGF-II receptors. Both the insulin and IGF-I receptors are heterotetramers joined by disulfide bonds. For both, the cytoplasmic portion of the $\beta$ subunits have tyrosine kinase domains as well as autophosphorylation sites. The IGF-II receptor (also called mannose-6-phosphate [M6P] receptor) is a single polypeptide chain with no kinase domain.

## Insulin-Like Growth Factor II Has Actions Similar to Those of Insulin-Like Growth Factor but Is Less Dependent on Growth Hormone

The physiology of IGF-II differs from that of IGF-I in a number of important respects. First, as noted earlier, the synthesis of IGF-II depends less on circulating GH than that of IGF-I. In pituitary dwarfism secondary to GH deficiency, the circulating concentration of IGF-I is decreased, but that of IGF-II is not. In states of excessive GH secretion, plasma IGF-I is reliably elevated, whereas plasma IGF-II is not.

Although IGF-II also binds to the IGF-I receptor, it preferentially binds to its own so-called IGF-II receptor. This IGF-II receptor consists of a single-chain polypeptide and is structurally very distinct from the IGF-I receptor (see Fig. 47–6). The IGF-II receptor lacks a tyrosine-kinase domain and does not undergo autophosphorylation in response to the binding of either IGF-II or IGF-I. The IGF-II receptor also binds mannose-6-phosphate (M6P), but at a site different from that for IGF-II binding, and the receptor's physiological role appears to be in processing mannosylated proteins by targeting them for lysosomal degradation. Thus, the term "IGF-II receptor" is somewhat of a misnomer; the IGF-II receptor's role in the physiological action of IGF-II is not clear.

Despite these differences, IGF-II does share with IGF-I (and also with insulin) the ability to promote tissue growth and cause acute hypoglycemia. These properties appear to be due to IGF-II's structural similarity to proinsulin and its ability to bind to the IGF-I receptor.

## Insulin and glucagon provide short-term regulation of plasma glucose levels

## Other hormones involved in the regulation of plasma glucose

Insulin and glucagon play a pivotal role in the fine regulation of plasma glucose levels—indeed, insulin is the only hormone capable of lowering plasma glucose, and glucagon is the most important hyperglycemic hormone. Nevertheless, a number of other agents also contribute to the maintenance of a stable blood glucose, as well as mobilizing glucose when necessary. These hormones include adrenal corticosteroids, growth hormone, the catecholamines, and the thyroid hormones.

**TABLE 18-4 SUMMARY OF GLUCOSE-COUNTERREGULATORY CONTROLS***

| | Glucagon | Epinephrine | Cortisol | Growth hormone |
|---|---|---|---|---|
| Glycogenolysis | X | X | | |
| Gluconeogenesis | X | X | X | X |
| Lipolysis | – | X | X | X |
| Inhibition of glucose uptake | – | – | X | X |

*All the processes listed on the left—glycogenolysis, gluconeogenesis, lipolysis, and inhibition of glucose uptake—are opposed to insulin's actions and are stimulated by one or more of the glucose-counterregulatory hormones in the table. An X indicates that the hormone stimulates the process; no X indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.*

"To a great extent insulin may be viewed as the "hormone of plenty." Its secretion and plasma concentration are increased during the absorptive period and decreased during postabsorption, and these changes are adequate to cause most of the metabolic changes associated with these periods. In addition, opposed in various ways to insulin's effects are the actions of four major glucose-counterregulatory controls—glucagon, epinephrine and the sympathetic nerves to the liver and adipose tissue, cortisol, and growth hormone (Table 18-4). Glucagon and the sympathetic nervous system are activated during the postabsorptive period (or in any other situation with hypoglycemia) and definitely play roles in preventing hypoglycemia, glucagon being the more important. The rates of secretion of cortisol and growth hormone are not usually coupled to the absorptive-postabsorptive pattern; nevertheless, their presence in the blood at basal concentrations is necessary for normal adjustment of lipid and carbohydrate metabolism to the postabsorptive period, and excessive amounts of either hormone cause abnormally elevated plasma glucose concentrations.

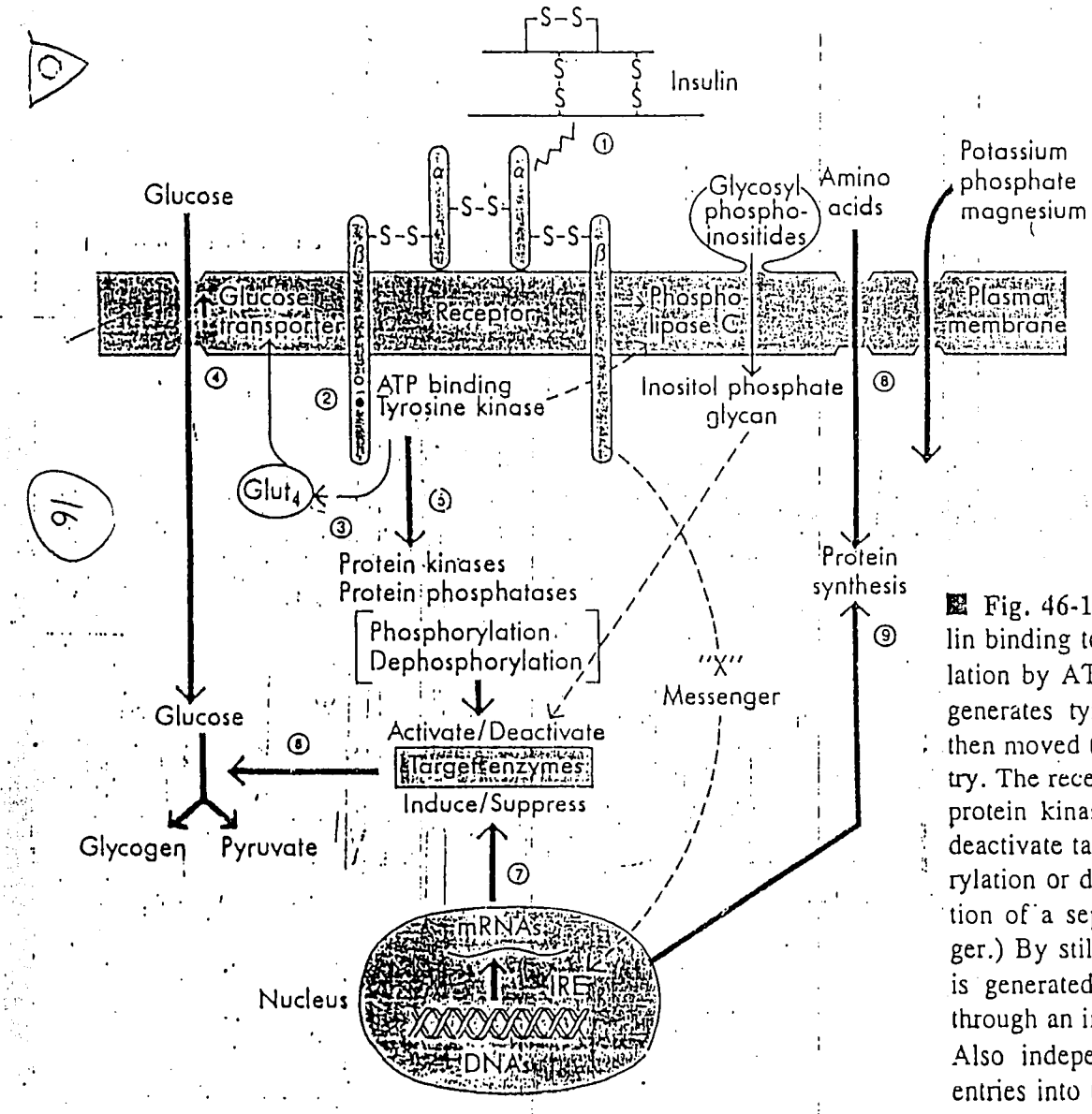



**Fig. 46-10** Mechanisms of insulin action on cells. Insulin binding to α-subunit of its receptor causes autophosphorylation by ATP of an intracellular β-subunit receptor site that generates tyrosine kinase activity. Glucose transporters are then moved to the plasma membrane and facilitate glucose entry. The receptor tyrosine kinase is presumed to phosphorylate protein kinases and phosphatases, which in turn activate or deactivate target enzymes of glucose metabolism by phosphorylation or dephosphorylation. (This may be aided by generation of a separate inositol phosphate glycan second messenger.) By still undefined mechanisms, a transcription factor(s) is generated that stimulates or represses gene transcription through an insulin response element (IRE) in DNA molecules. Also independently potassium, magnesium, and phosphate entries into the cell are facilitated.

Table 23.13 Principal actions of insulin on cells

| |
|---|
| *Membrane effects* |
| Uptake of glucose increased |
| Uptake of amino acids increased |
| Uptake of fatty acids increased |
| Uptake of $Mg^{2+}$ and $K^{+}$ increased |
| *Metabolic effects* |
| Increased synthesis of DNA and RNA |
| Increased protein synthesis |
| Increased synthesis of glycogen (in liver and muscle) |
| Increased synthesis of triglycerides (in adipose tissue) |
| Increased synthesis of cholesterol (in liver and gut) |
| Increased fatty acid synthesis (in liver) |
| Decreased protein breakdown (in muscle) |
| Decreased glycogenolysis (in liver) |
| Decreased gluconeogenesis (in liver and kidney) |
| Decreased ketone production (in liver) |
| Decreased triglyceride breakdown (in adipose tissue) |

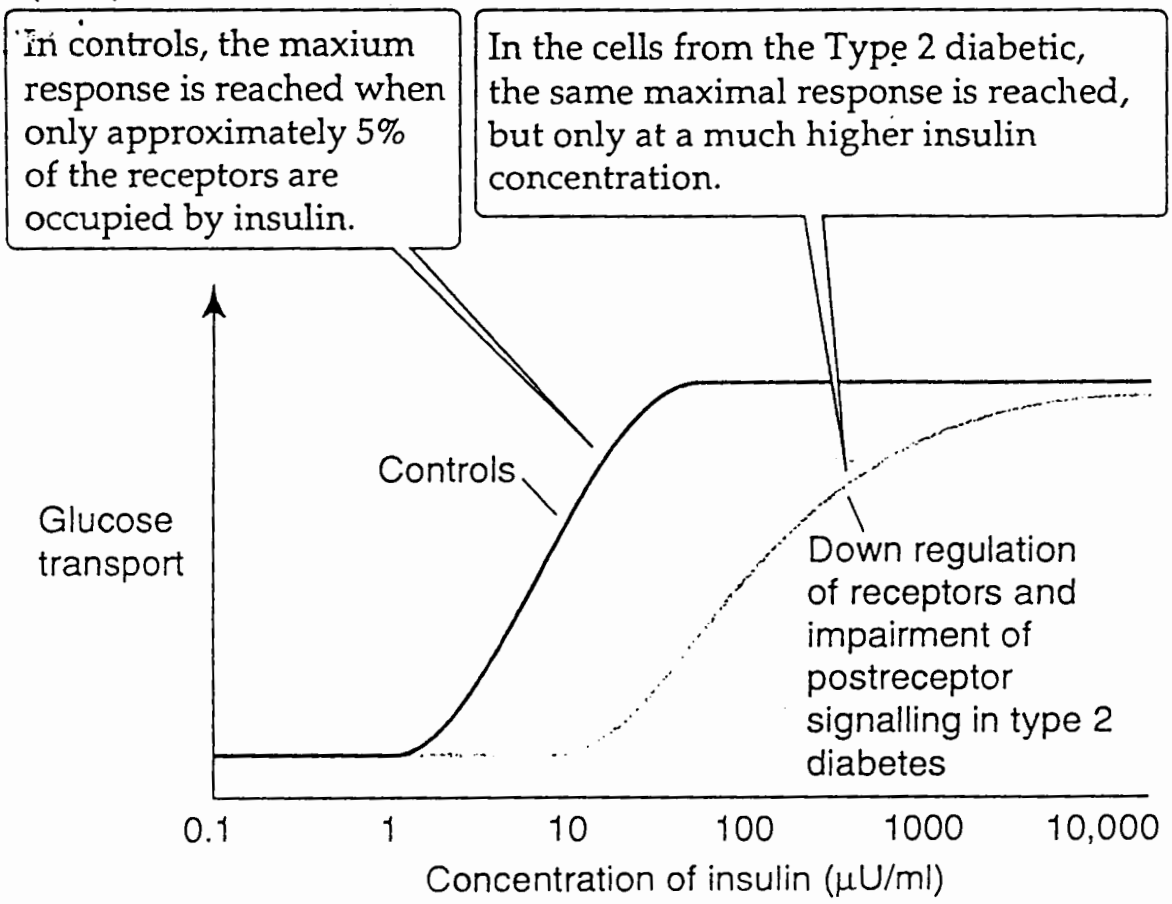



FIGURE 50–7. Response to insulin of normal and "downregulated" adipocytes.

Table 7.6
Biological effects of insulin

A. On carbohydrate metabolism
   1. Reduces rate of release of glucose from liver
      a. by inhibiting glycogenolysis.
      b. by stimulating glycogen synthesis.
      c. by stimulating glucose uptake.
      d. by stimulating glycolysis.
      e. by indirectly inhibiting gluconeogenesis via inhibition of fatty acid mobilization from adipose tissue.
   2. Increases rate of uptake of glucose into all insulin-sensitive tissues, notably muscle and adipose tissue
      a. directly, by stimulating glucose transport across the plasma membrane.
      b. indirectly, by reducing plasma-free fatty acid levels.

B. On lipid metabolism
   1. Reduces rate of release of free fatty acids from adipose tissue.
   2. Stimulates de novo fatty acid synthesis and also conversion of fatty acids to triglycerides in liver.

C. On protein metabolism
   1. Stimulates transport of free amino acids across the plasma membrane in liver and muscle.
   2. Stimulates protein biosynthesis and reduces release of amino acid from muscle.

D. On ion transport

E. On growth and development

Table 19–5. Principal actions of insulin.

**Adipose tissue**

1. Increased glucose entry
2. Increased fatty acid synthesis
3. Increased glycerol phosphate synthesis
4. Increased triglyceride deposition
5. Activation of lipoprotein lipase
6. Inhibition of hormone-sensitive lipase
7. Increased $K^+$ uptake

**Muscle**

1. Increased glucose entry
2. Increased glycogen synthesis
3. Increased amino acid uptake
4. Increased protein synthesis in ribosomes
5. Decreased protein catabolism
6. Decreased release of gluconeogenic amino acids
7. Increased ketone uptake
8. Increased $K^+$ uptake

**Liver**

1. Decreased ketogenesis
2. Increased protein synthesis
3. Increased lipid synthesis
4. Decreased glucose output due to decreased gluconeogenesis and increased glycogen synthesis

**General**

1. Increased cell growth

Table 19–3. Effect of insulin on glucose uptake in tissues in which it has been investigated.

| |
|---|
| **Tissues in which insulin facilitates glucose uptake** |
| Skeletal muscle |
| Cardiac muscle |
| Smooth muscle |
| Adipose tissue |
| Leukocytes |
| Crystalline lens of the eye |
| Pituitary |
| Fibroblasts |
| Mammary gland |
| Aorta |
| A cells of pancreatic islets |
| **Tissues in which insulin does not facilitate glucose uptake** |
| Brain (except probably part of hypothalamus) |
| Kidney tubules |
| Intestinal mucosa |
| Red blood cells |

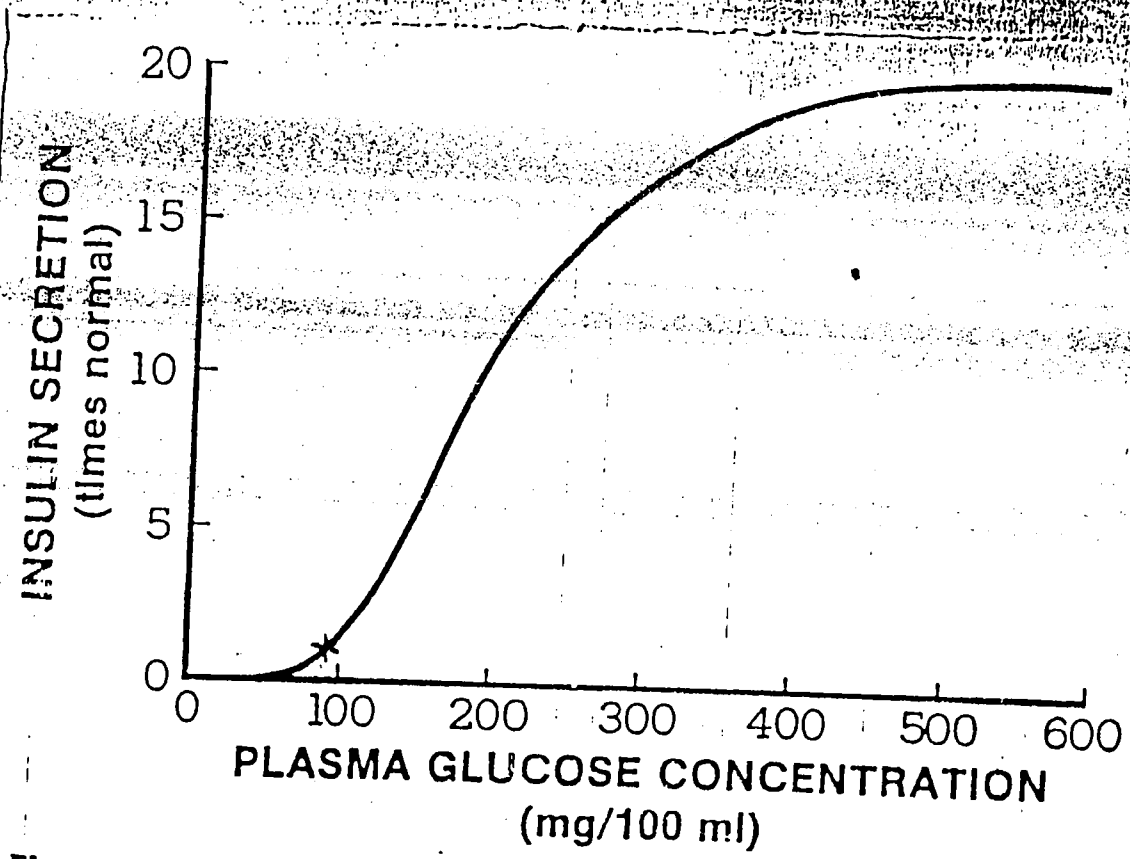



**Figure 78–8.** Approximate increase in insulin secretion at different plasma glucose levels.

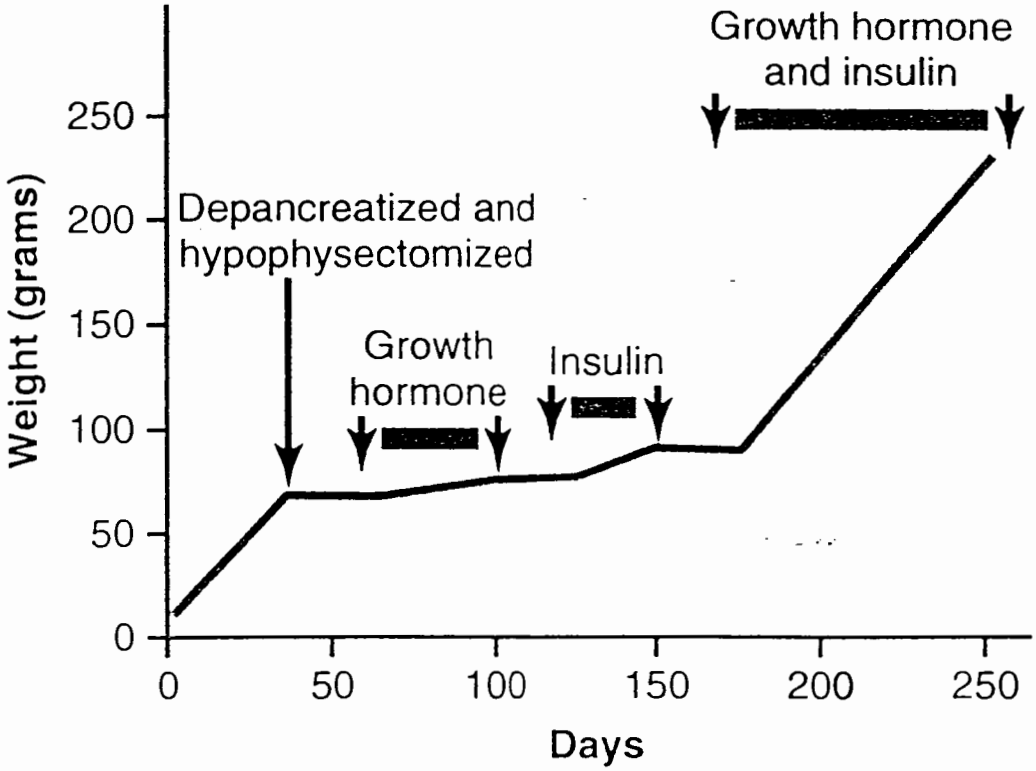



**Figure 78-6** Effect of growth hormone, insulin, and growth hormone plus insulin on growth in a depancreatized and hypophysectomized rat.

## Insulin and Growth Hormone Interact Synergistically to Promote Growth.

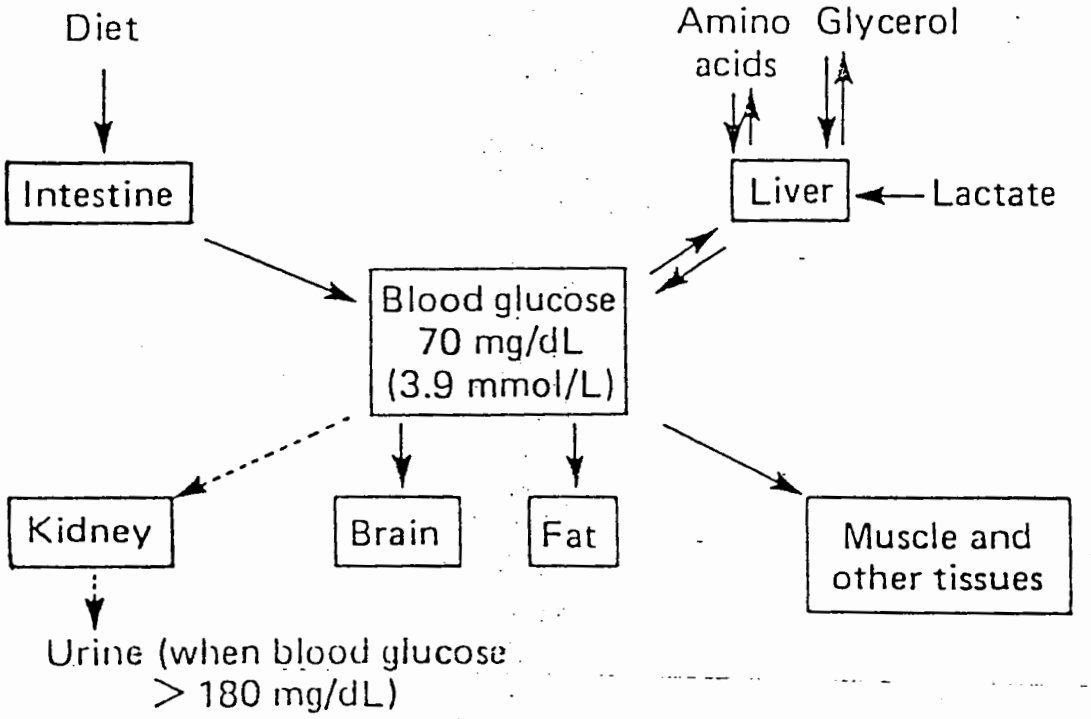



**Figure 17–14.** Blood glucose homeostasis, illustrating the glucostatic function of the liver.

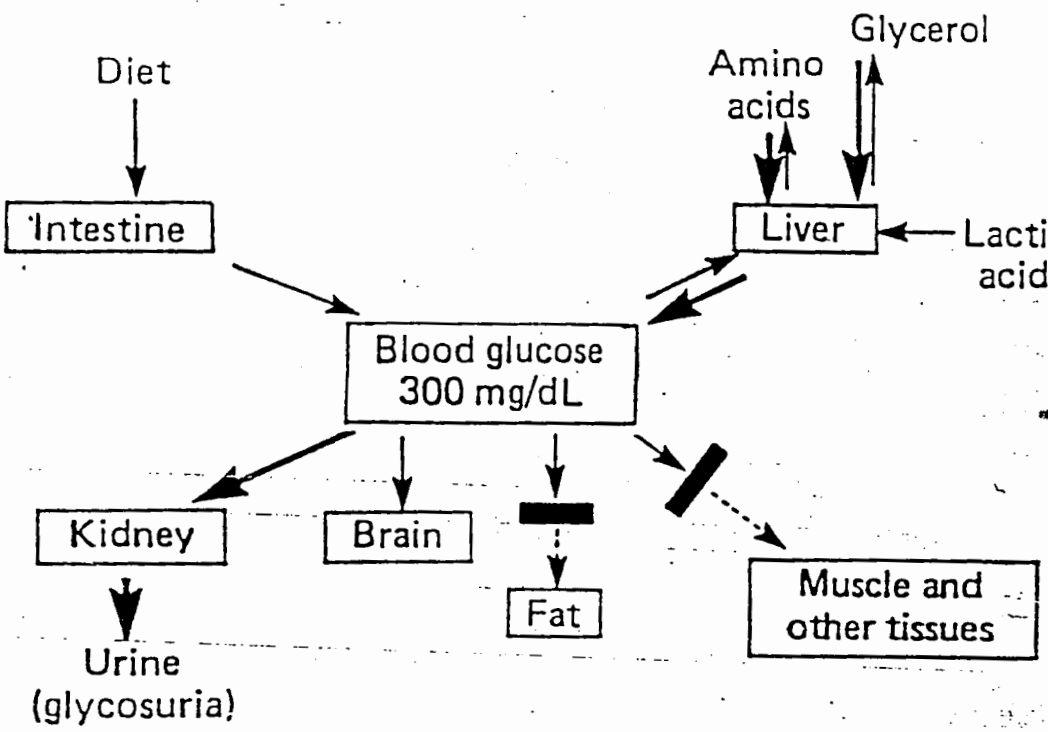



**Figure 19–7.** Disordered blood glucose homeostasis in insulin deficiency. Compare with Fig 17–14. The heavy arrows indicate reactions that are accentuated. The rectangles across arrows indicate reactions that are blocked.

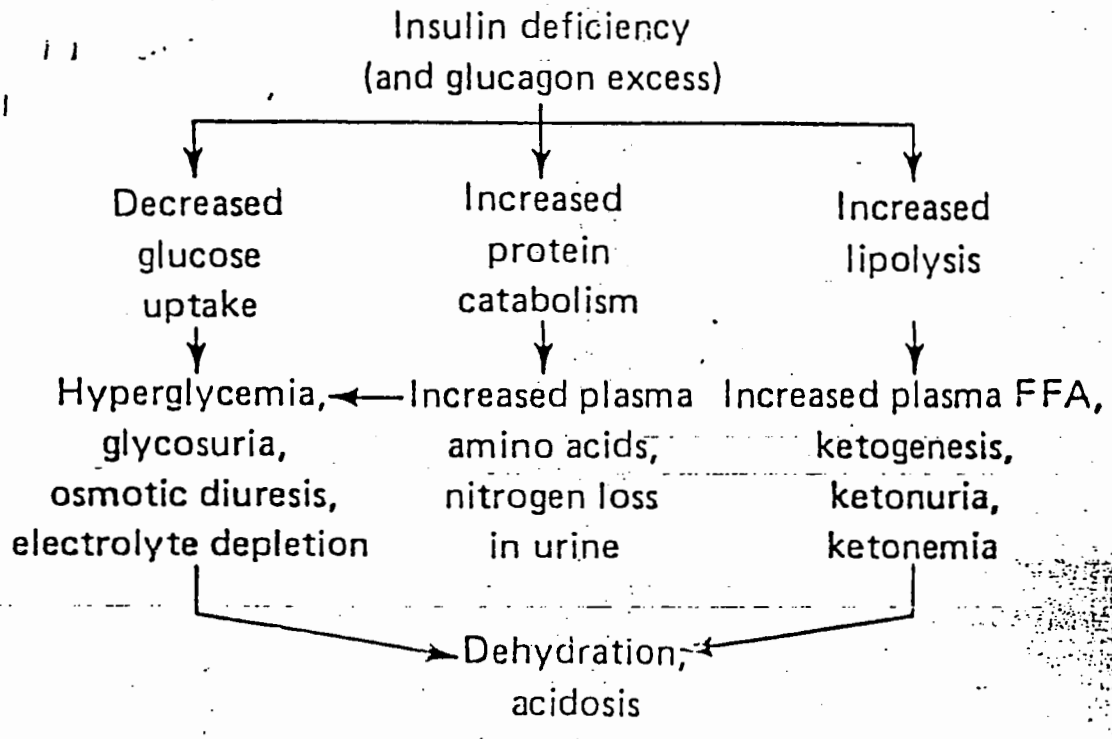



**Figure 19–10.** Effects of insulin deficiency. (Courtesy of RJ Havel.)

Table 19-2. Types of human diabetes mellitus.

| Type | Other Names |
|---|---|
| Type I | Insulin-dependent diabetes (IDDM).<br>Juvenile diabetes.<br>Ketosis-prone diabetes. |
| Type II | Non-insulin-dependent diabetes (NIDDM).<br>Maturity-onset diabetes.<br>Ketosis-resistant diabetes. |
| Diabetes associated with other conditions | Examples include diabetes due to pancreatoectomy or pancreatic disease; diabetes due to defective forms of insulin or insulin receptors; and diabetes in patients with Cushing's syndrome, acromogaly, or other endocrine diseases. |

Table 19–10. Types of human diabetes mellitus.

| Type | Other Names |
|---|---|
| Type I | Insulin-dependent diabetes (IDDM).<br>Juvenile diabetes.<br>Ketosis-prone diabetes. |

*Type I diabetes mellitus, or insulin-dependent diabetes mellitus (IDDM),* was formerly known as *juvenile-onset diabetes.* Type I diabetes develops suddenly, usually before the age of 15 years, and often reflects pathology of the β islet cells resulting from viral infection or an autoimmune response. Type I diabetics totally lack insulin activity, and their disease is extremely difficult to control. Insulin injections must be given several times daily to manage ketosis and, to a lesser extent, hyperglycemia. Because of the early onset of their disease, type I diabetics typically exhibit long-term vascular and neural problems. Complications resulting from vascular problems include atherosclerosis, strokes, heart attacks, gangrene, and blindness; consequences of neuropathies include loss of sensation, impaired bladder function, and impotence.

| Type II | Non-insulin-dependent diabetes (NIDDM). Maturity-onset diabetes. Ketosis-resistant diabetes. |
|---|---|

*Type II diabetes, or non-insulin-dependent diabetes mellitus (NIDDM)* was formerly called *maturity-onset diabetes* because it occurs mostly after the age of 40 years and is increasingly common with age. Heredity or a familial predisposition is particularly striking in this diabetic group; if an identical twin has type II diabetes mellitus, the probability that the other twin will have the disease is 100%. Although most type II diabetics produce insulin, the amount is inadequate or there is some abnormality of the insulin receptors. Type II diabetics are almost always overweight and account for over 90% of the known cases of diabetes mellitus. Ketosis is not a major problem for this group, and in many cases the symptoms can be managed solely by diet and exercise. Weight control is very important, because obesity alone causes the insulin receptors to become less sensitive to insulin.

28

| | |
|---|---|
| Diabetes associated with other conditions | Examples include diabetes due to pancreatoectomy or pancreatic disease; diabetes due to defective forms of insulin or insulin receptors; and diabetes in patients with Cushing's syndrome, acromogaly, or other endocrine diseases. |

①The number or the affinity, or both, of insulin receptors is affected by insulin and other hormones, exercise, food, and other factors.②Exposure to increased amounts of insulin decreases receptor concentration (down regulation), and exposure to decreased insulin increases the affinity of the receptors.③The number of receptors per cell is increased in starvation and decreased in obesity and acromegaly. ④The affinity of the receptors is increased in adrenal insufficiency and decreased by excess glucocorticoids

## Obesity

Obesity is the most common and most expensive nutritional problem in the USA. A convenient and reliable indicator of body fat is the **body mass index** (BMI), which is the body weight (in kilograms) divided by the square of the height (in meters). Values above 25 are abnormal. Individuals with values of 25–30 are overweight, and those with values > 30 are obese. In the USA, 55% of the population are overweight and 22% are obese. The incidence of obesity is also increasing in other countries. Indeed, the Worldwatch Institute has estimated that although starvation continues to be a problem in many parts of the world, the number of overweight people in the world is now as great as the number of underfed.

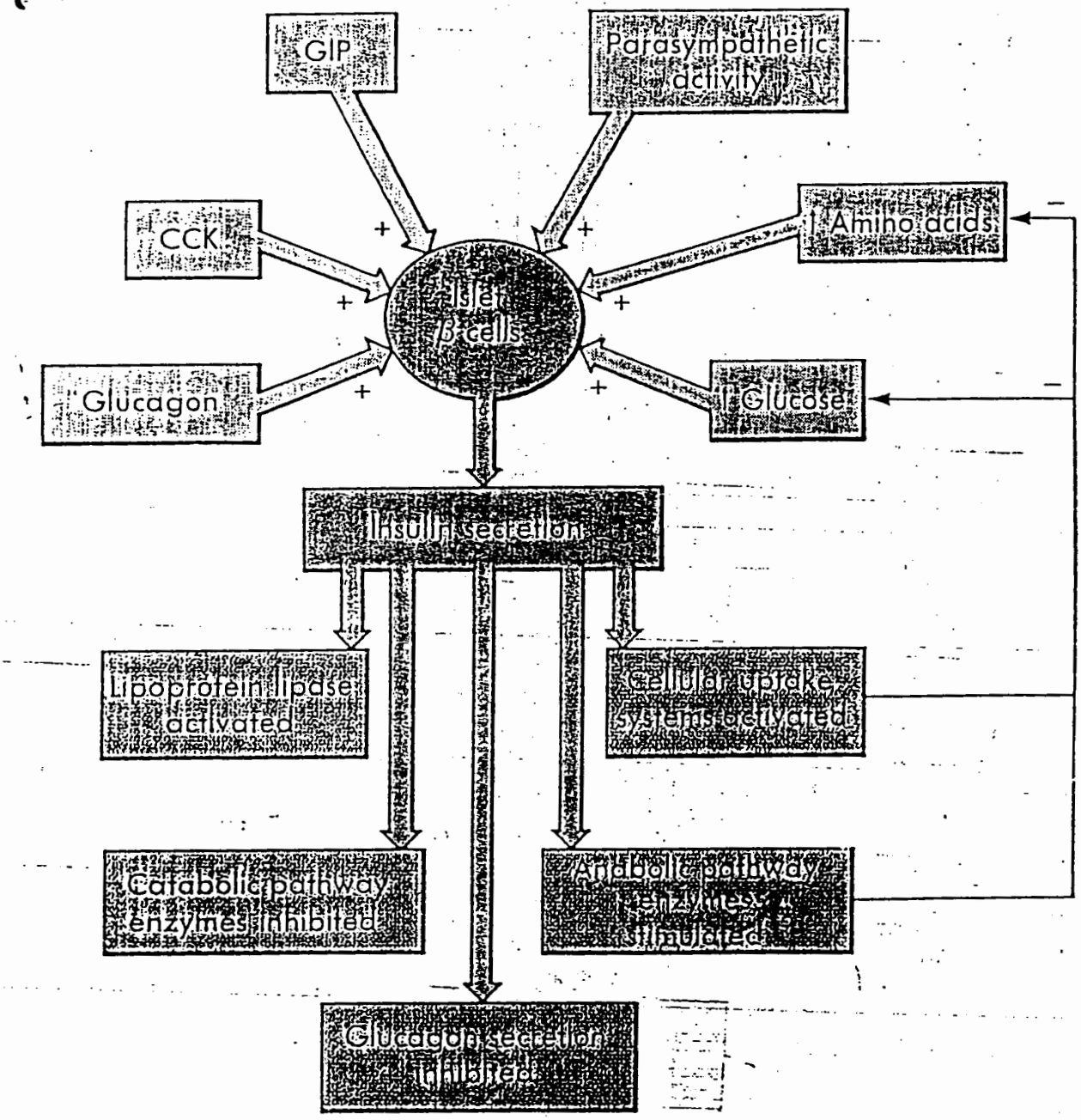



*FIGURE 23-2*
Inputs to beta cells and effects of insulin, including negative feedback on glucose and amino-acid levels.

**Table 78-1** Factors and Conditions That Increase or Decrease Insulin Secretion

| Increase Insulin Secretion | Decrease Insulin Secretion |
|---|---|
| Increased blood glucose | Decreased blood glucose |
| Increased blood free fatty acids | Fasting |
| Increased blood amino acids | Somatostatin |
| Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide) | α-Adrenergic activity |
| | Leptin |
| Glucagon, growth hormone, cortisol | |
| Parasympathetic stimulation; acetylcholine | |
| β-Adrenergic stimulation | |
| Insulin resistance; obesity | |
| Sulfonylurea drugs (glyburide, tolbutamide) | |

⊛Glucagon is a single peptide of 29 a.a. with m.w of 3500. Biologic activity resides in 1–6 a.a.

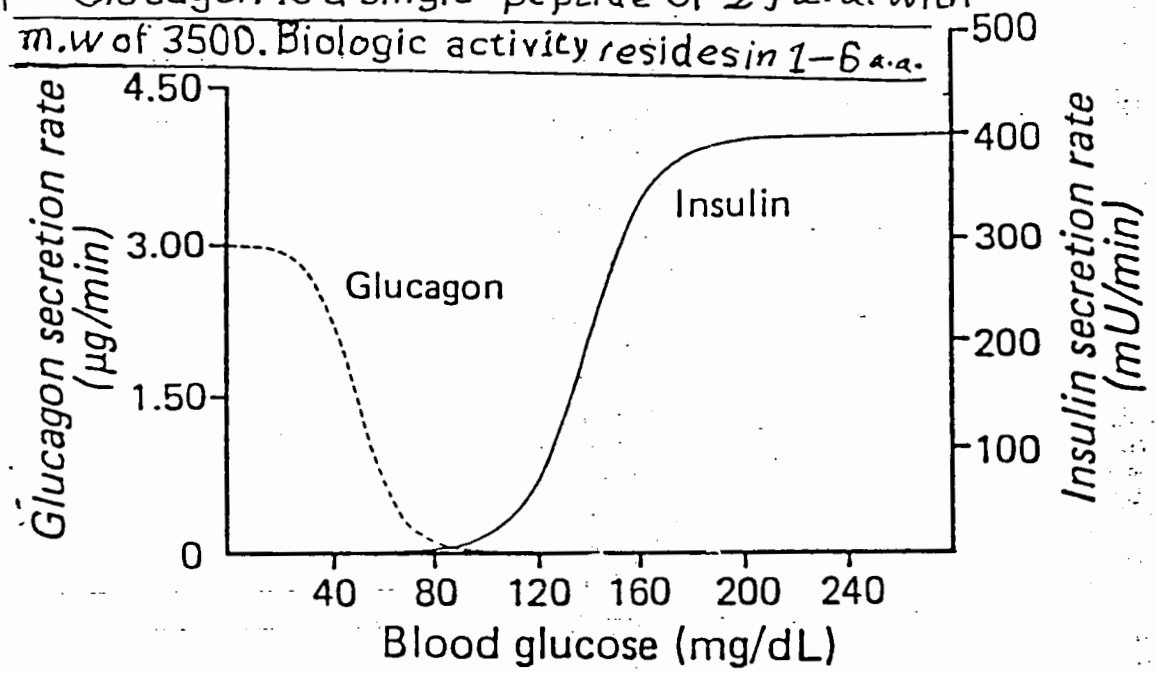



**Figure 19–12.** Mean rates of insulin and glucagon delivery from an artificial pancreas at various blood glucose levels. The device was programmed to establish and maintain normal blood glucose in insulin-requiring diabetic humans, and the values for hormone output approximate the output of the normal human pancreas. The shape of the insulin curve also resembles the insulin response of incubated B cells to graded concentrations of glucose. (Reproduced, with permission, from Marliss EB et al: Normalization of glycemia in diabetics during meals with insulin and glucagon delivery by the artificial pancreas. *Diabetes* 1977;26:663.)

**Table 7.7**
Factors influencing glucagon release

| Stimulation | Inhibition |
|---|---|
| Amino acids | Glucose |
| Gastrointestinal polypeptide hormones | Insulin |
| Catecholamines (exercise) | Free fatty acids |
| Growth hormone | |
| Glucocorticoids | |

## Action of glucagon on target tissues

It has been established that glucagon is capable of producing the following actions.

1. Glycogenolysis in the liver.
2. Inhibition of glycogen synthesis in the liver.
3. Gluconeogenesis in the liver.
4. Lipolysis in adipose tissue.
5. Stimulation of insulin release from $\beta$ cells.
6. Stimulation of catecholamine release.
7. A positive inotropic effect on the heart.

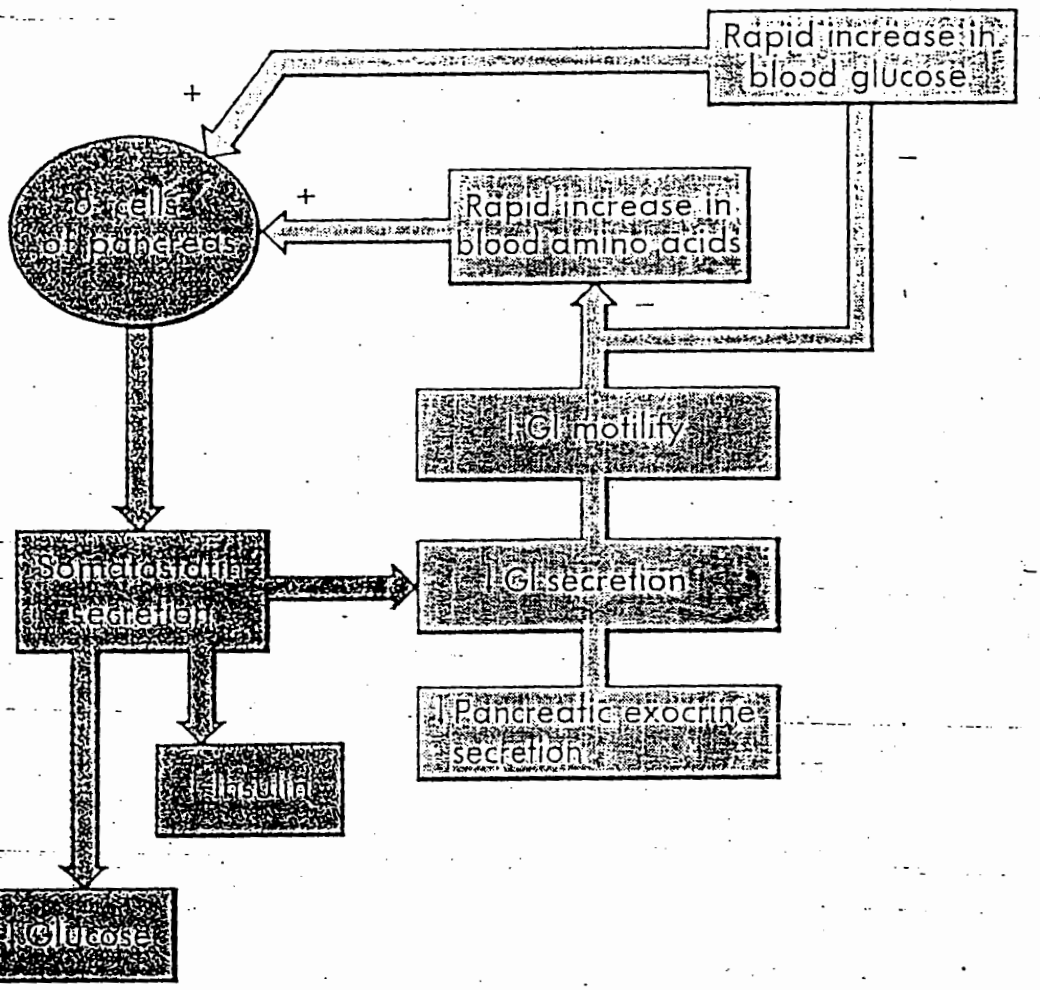



*FIGURE 23-7*

Inputs to delta cells and effects of somatostatin, including negative feedback, which reduces entry of glucose and amino acids into the circulation.

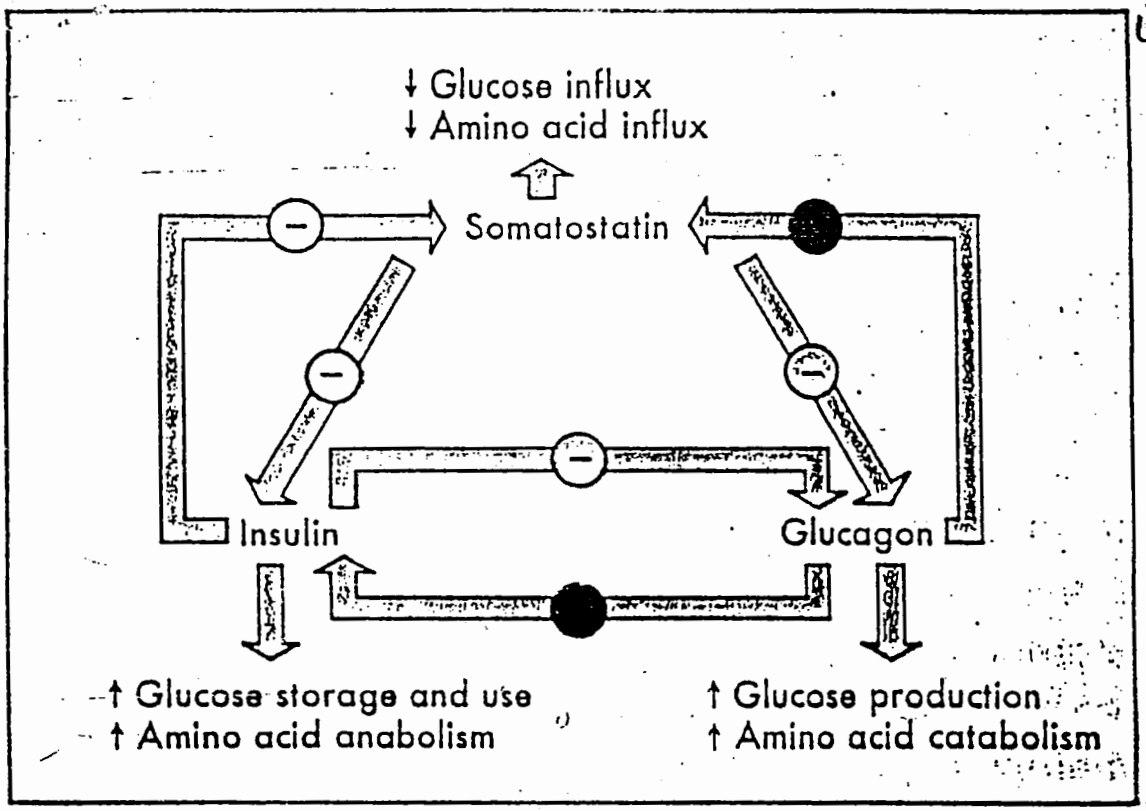



**FIGURE 37-8** The interrelationships between somatostatin, insulin, and glucagon effects on each other's secretions and their effects on glucose and amino acid metabolism. (Modified from Unger RH et al. Reproduced with permission from the *Annual Review of Physiology,* volume 40. Copyright © 1978 by Annual Reviews, Inc.)

## Cholecystokinin-Pancreozymin

It was formerly thought that a hormone called cholecystokinin produced contraction of the gallbladder whereas a separate hormone called pancreozymin increased the secretion of pancreatic juice rich in enzymes. It is now clear that a single hormone secreted by cells in the mucosa of the upper small intestine has both activities, and the hormone has therefore been named **cholecystokinin-pancreozymin.** It is also called **CCK-PZ** or, most commonly, **CCK.**

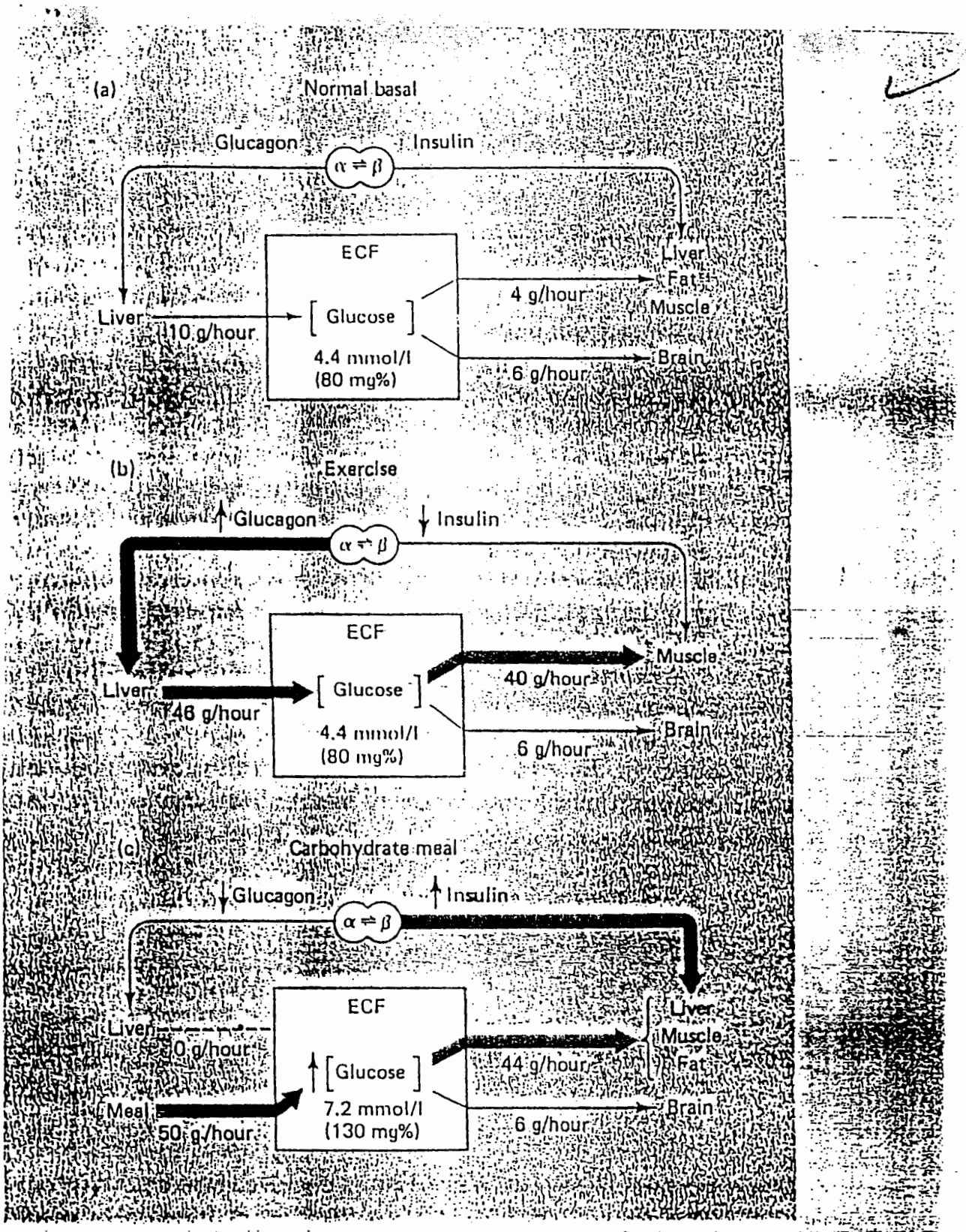



**Fig. 4.7** A diagrammatic representation of the patterns of glucagon and insulin release at rest (**A**), during exercise (**B**) and following a meal of carbohydrate (**C**) and the consequential changes in glucagon distribution. (From Unger, R. H. (1976) Diabetes **25**, 136.)

## TABLE 35.2 Factors Regulating Glucagon Secretion From the Pancreas

| | |
|---|---|
| Stimulatory agents or conditions | Hypoglycemia |
| | Amino acids |
| | Acetylcholine |
| | Norepinephrine |
| | Epinephrine |
| Inhibitory agents or conditions | Fatty acids |
| | Somatostatin |
| | Insulin |

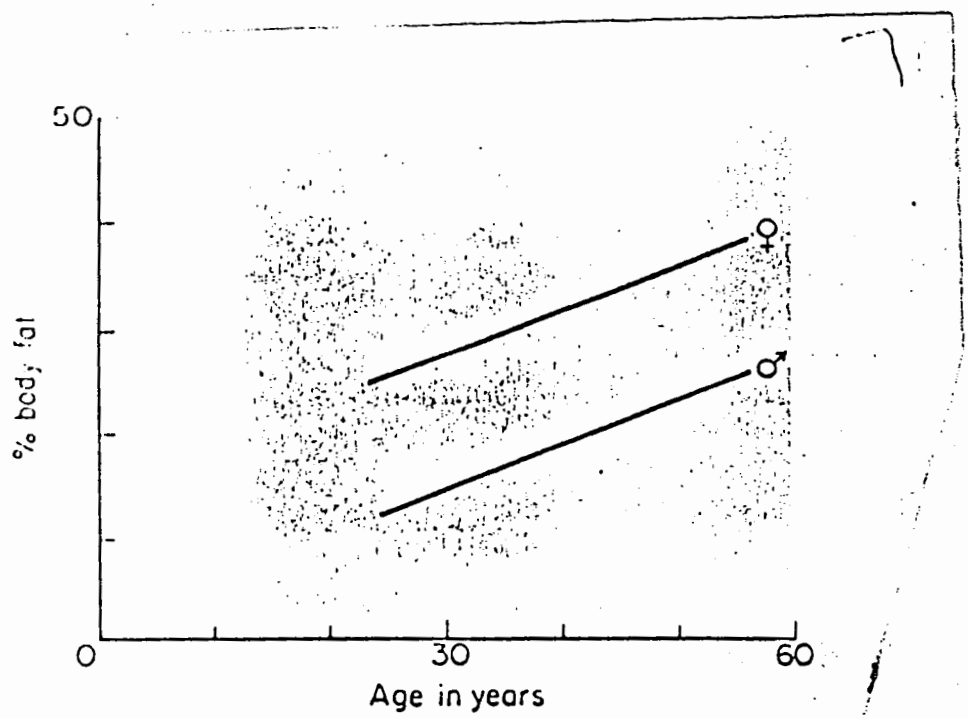
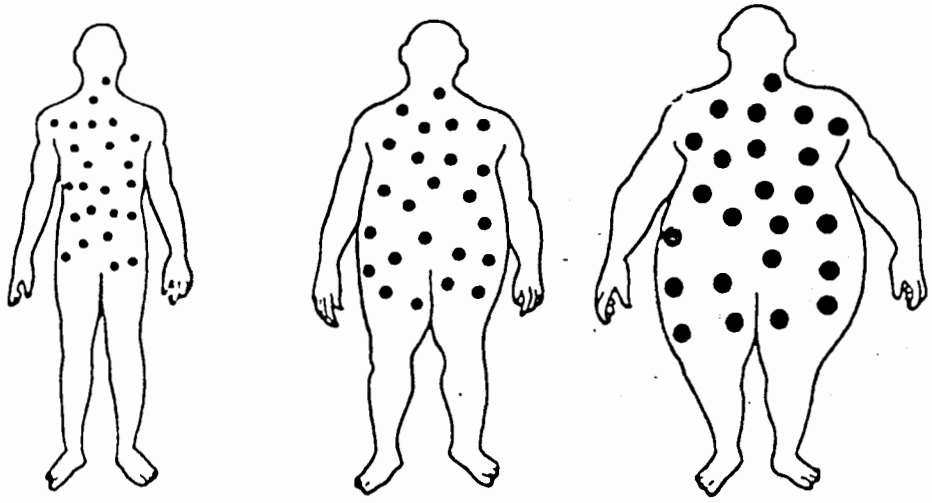



Fig. 6.21 Body fat at different ages in males and females.

**Obesity**—body weight more than 20% above some desirable standard due to an excessive accumulation of adipose tissue—affects one-third of the adult population in the United States. (An athlete may be *overweight* due to higher-than-normal amounts of muscle tissue without being obese.) Even moderate obesity is hazardous to health; it is implicated as a risk factor in cardiovascular disease, hypertension, pulmonary disease, non-insulin-dependent diabetes mellitus, arthritis, certain cancers (breast, uterus, and colon), varicose veins, and gallbladder disease. Also, loss of body fat in obese individuals has been shown to elevate HDL cholesterol, the type associated with prevention of cardiovascular disease.



| Body weight | 165 lb | 227 lb | 328 lb |
|---|---|---|---|
| Fat cell size | 0.2 μg/cell | 0.6 μg/cell | 0.9 μg/cell |
| Fat cell number | 75 billion | 75 billion | 75 billion |

**Fig. 6.22** In obesity the number of fat cells (the number is determined in infancy) stays constant, but the fat content of each increases (after Stollerman).

**TABLE 78-2**

Clinical Characteristics of Patients with Type I and Type II Diabetes Mellitus

| Feature | Type I | Type II |
|---|---|---|
| Age at onset | Usually <20 years | Usually >40 years |
| Body mass | Low (wasted) to normal | Obese |
| Plasma insulin | Low or absent | Normal to high |
| Plasma glucagon | High, can be suppressed | High, resistant to suppression |
| Plasma glucose | Increased | Increased |
| Insulin sensitivity | Normal | Reduced |
| Therapy | Insulin | Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin |

*Insulin-dependent diabetes (IDDM)
Juvenile diabetes.

*Non-insulin-dependent diabetes (NIDDM).
Maturity-onset diabetes.

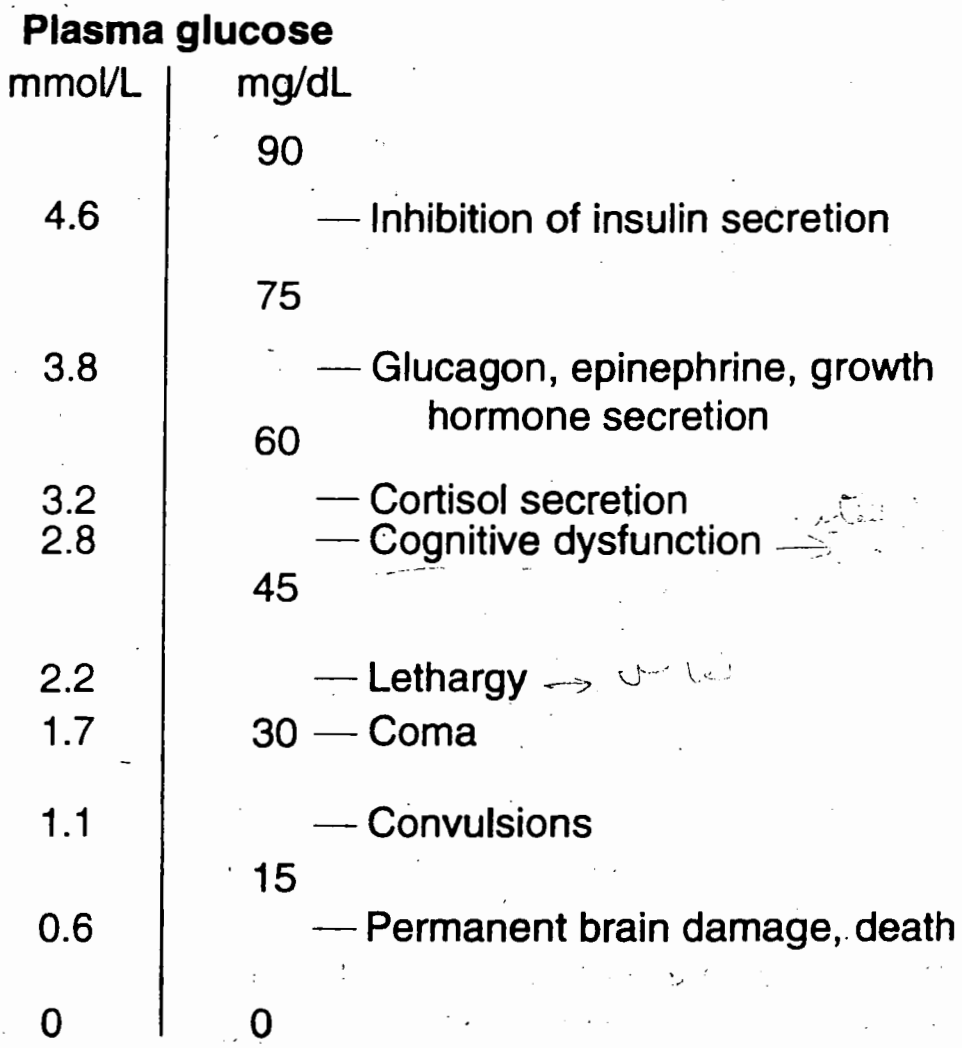



***Figure 19–11.*** Plasma glucose levels in arterialized venous blood at which various effects of hypoglycemia appear.

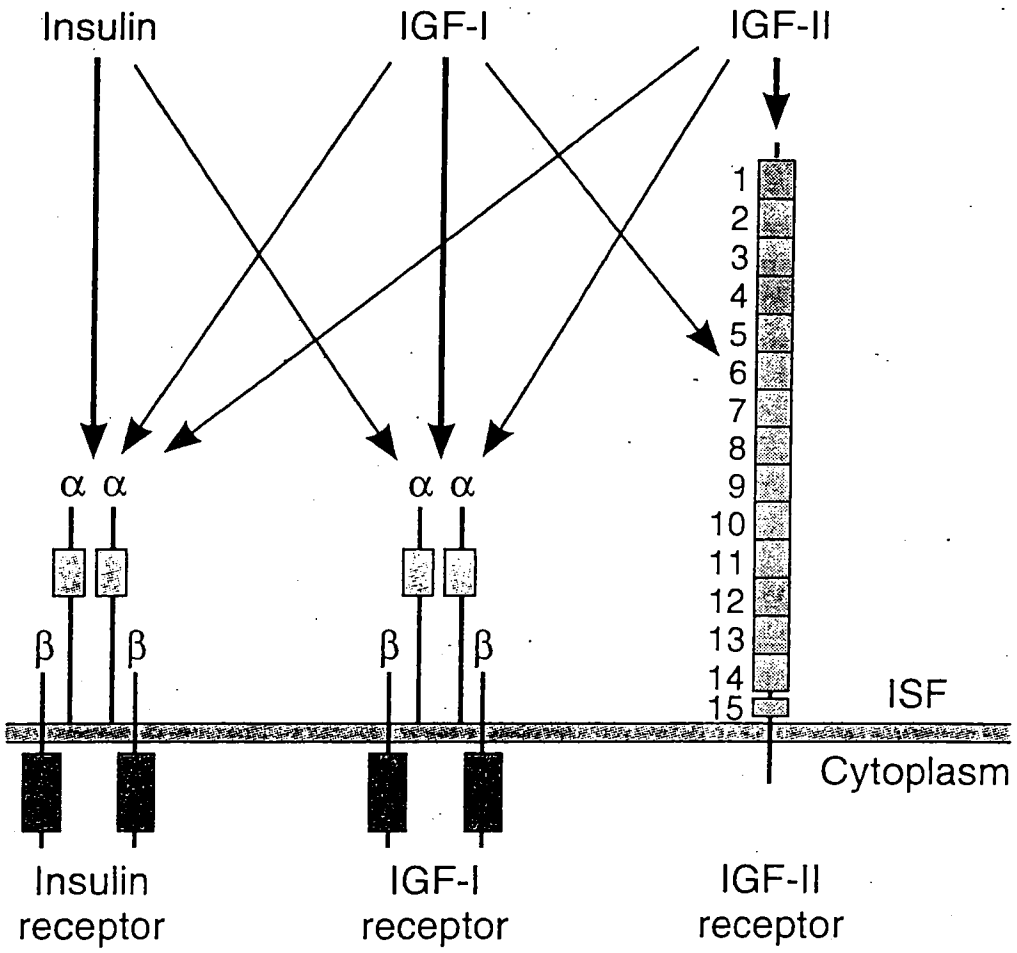



***Figure 19–6.*** Insulin, IGF-I, and IGF-II receptors. Each hormone binds primarily to its own receptor, but insulin also binds to the IGF-I receptor, and IGF-I and IGF-II bind to all three. The dark-colored boxes are intracellular tyrosine kinase domains. Note the marked similarity between the insulin receptor and the IGF-I receptor; also note the 15 repeat sequences in the extracellular portion of the IGF-II receptor.

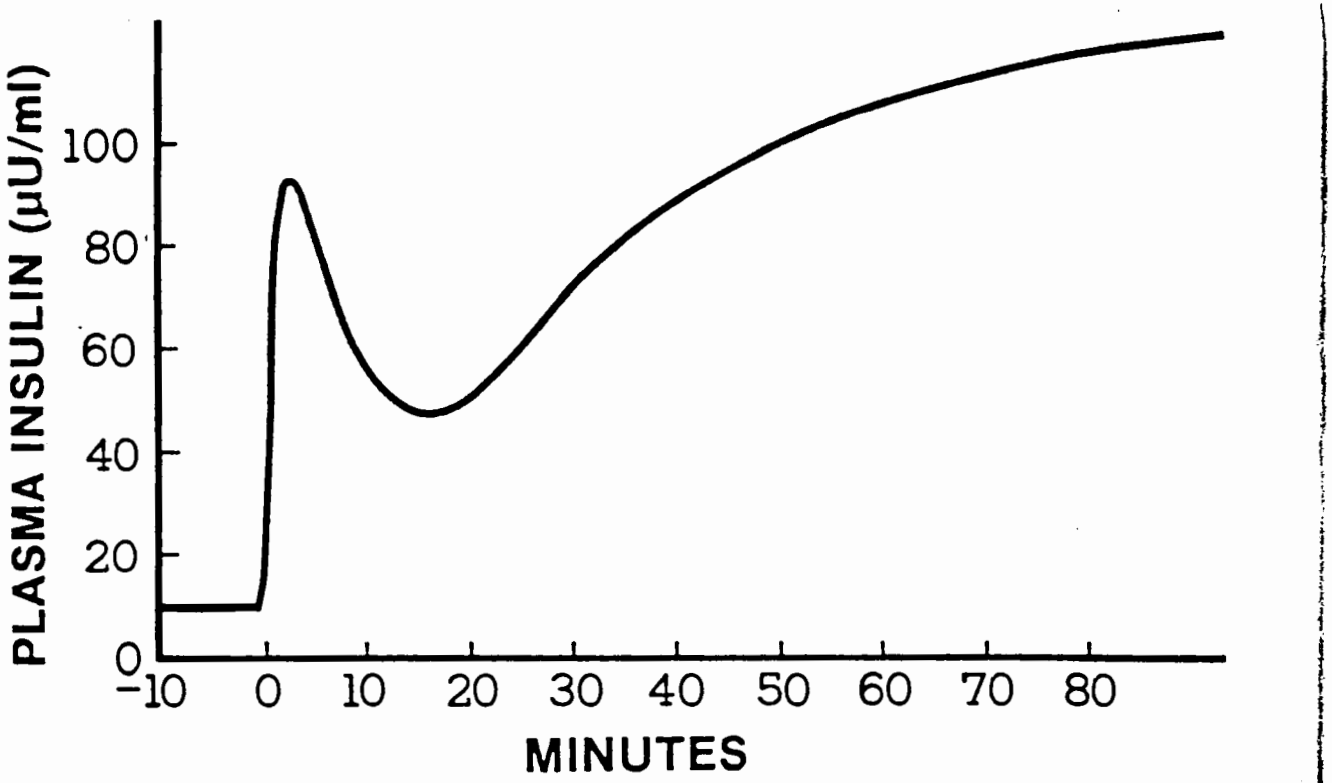



**Figure 78–7.** Increase in plasma insulin concentration following a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.