Abstract: The human body represents one of a highly evolved dynamical system. In it, one can identify systems or subsystems which are analogous to many engineered controlled systems. Perturbations of some of these regulated control systems lead to what are known as medical emergencies in clinical parlance. These systems can be classified based on the response time due to the complex feedback loops, of (a) micro to milliseconds (eg: the neural reflexes, functions of the autonomic nervous system, the visual-vestibular system of maintaining balance etc), (b) seconds to minutes (eg: glucose homeostasis, disruption of which lead to diabetic ketoacidosis or hyperosmolar coma, homeostasis of the cardiovascular system, perturbations of which lead to acute coronary syndromes, cardiac arrhythmias etc), and (c) hours to days (eg: homeostasis of the immune system, perturbations of which lead to infectious or autoimmune diseases. We are building and defining a working hypothesis of such systems at the clinician level and attempting to learn the principles of efficiency. The biochemical regulation of blood glucose homeostasis will be addressed in detail from the perspective of clinical management, and parallels to control theory will be attempted.

CONTROL SYSTEMS IN MEDICAL PRACTICE

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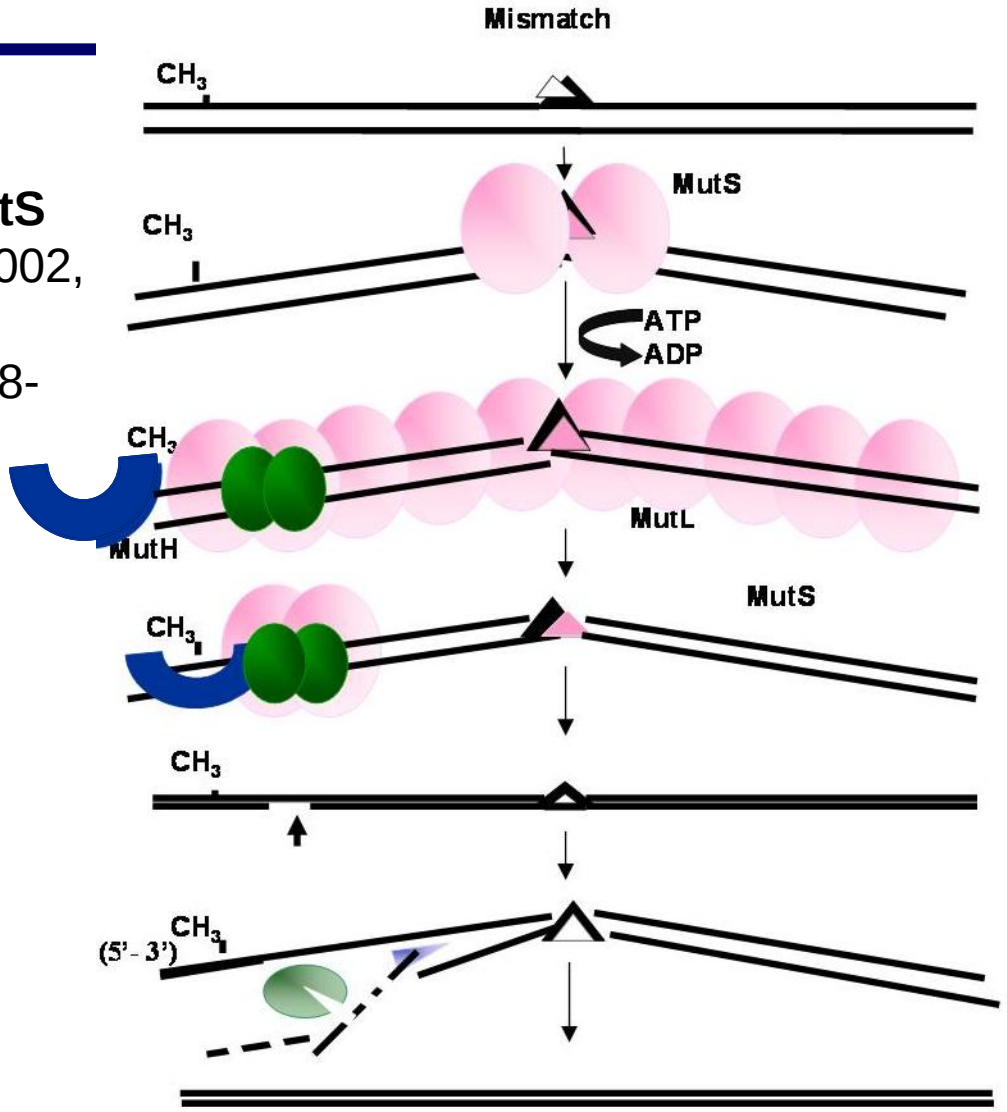
Illustration of the mechanism of Mismatch Repair in *E coli*

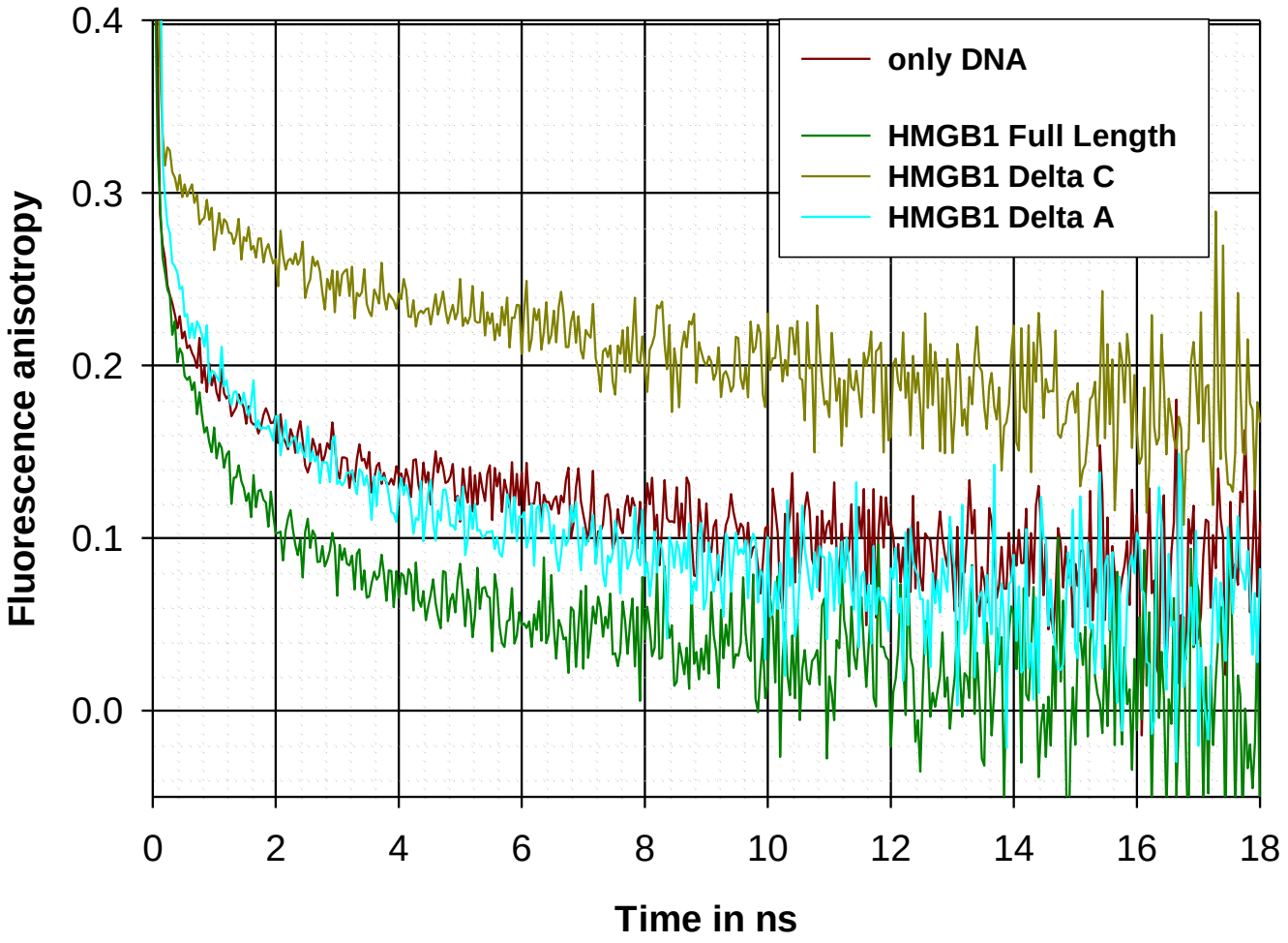
Mismatch Recognition by **MutS** (Joshi A et al. Biochemistry 2002, 41, 3654-3666)(Nag N et al. FEBS Letters 2005, 272, 6228-43)

Strand discrimination by strand specific nicking by **MutH**

Directional **(?)** Unwinding by **UvrD** and Directional **(?)** Excision by Exonucleases **ExoI/VII/X** or **RecJ**

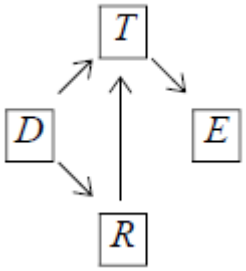


HMGB1 and deletion mutants with picogreen bound to supercoiled DNA

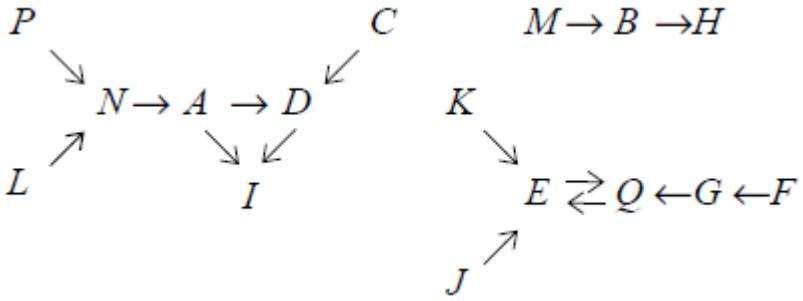


Aims:

1. Elaboration of the “need”
2. Few examples of regulatory system abnormalities encountered in the clinic
3. Distinction between systems based on interventional relevance
4. Basic analogies with theory and probable course.



Diagrams of immediate effects



Kinematic graphs

Levels of Evidence: Therapy/Prevention/Etiology/Harm:
From the Centre for Evidence-Based Medicine, Oxford

1a:	Systematic reviews (with homogeneity) of randomized controlled trials
1a-:	Systematic review of randomized trials displaying worrisome heterogeneity
1b:	Individual randomized controlled trials (with narrow confidence interval)
1b-:	Individual randomized controlled trials (with a wide confidence interval)
1c:	All or none randomized controlled trials
2a:	Systematic reviews (with homogeneity) of cohort studies
2a-:	Systematic reviews of cohort studies displaying worrisome heterogeneity
2b:	Individual cohort study or low quality randomized controlled trials (<80% follow-up)
2b-:	Individual cohort study or low quality randomized controlled trials (<80% follow-up / wide confidence interval)
2c:	'Outcomes' Research; ecological studies
3a:	Systematic review (with homogeneity) of case-control studies
3a-:	Systematic review of case-control studies with worrisome heterogeneity
3b:	Individual case-control study
4:	Case-series (and poor quality cohort and case-control studies)
5:	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

The Larvol Group

- Market intelligence tracking for the pharmaceutical industry
  - Subscription services with customized monitoring
  - Database development and other support services

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MARKET INTELLIGENCE REPORT: METASTATIC BREAST CANCER

Jan 10 - 16, 2010; Issue 7

Note: Based on public sources only

Work in Progress

For content clarification or elaboration: questions@larvol.com [No extra cost]

Sections (Hyperlinked)

Blue Font = News from Current Week

⬆: Positive Impact ⬇: Negative Impact
(Negative or positive impact for company/product discussed in given article rather than perspective of client)

Weekly Highlights *(also highlighted in yellow in this report)*

- ⬆Prevention of aromatase inhibitor-induced bone loss using risedronate: The SABRE trial *(J Clin Oncol)* - Jan 13 [**Arimidex (anastrozole)** / Roche; P3, N=237; Treatment with anastrozole + risedronate resulted in a significant increase in lumbar spine and total hip BMD vs. treatment with anastrozole + placebo; P3 data]
- **Bevacizumab** in metastatic breast cancer: A meta-analysis of randomized controlled trials *(Breast Cancer Res Treat)* - Jan 12 [**Avastin (bevacizumab)** / Genentech (Roche); N=3,163; Combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in PFS compared with chemotherapy alone (HR=0.70, 95% CI 0.60-0.82, p=9.3 x 10(-6)) and ORR (RR=1.26, 95% CI 1.17-1.37, p=9.96 x 10(-9)); Meta-analysis]
- Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: Results from NSABP B-14 and NSABP B-20 *(J Clin Oncol)* - Jan 13 [P3, N=895; In **tamoxifen**-treated patients, loco-regional recurrence was significantly associated with recurrence score risk groups (p<0.001); P3 biomarker data]
- 17ss-Hydroxysteroid dehydrogenase type 1 as predictor of **tamoxifen** response in premenopausal breast cancer *(Eur J Cancer)* - Jan 12 [N=564; Women with HR+ve tumors, who had low levels of 17HSD1, had a 43% reduced risk of recurrence, when treated with **tamoxifen**; Biomarker data]
- ⬆Oral combination chemotherapy with **capecitabine** and **cyclophosphamide** in patients with metastatic breast cancer: A phase II study *(Anticancer Drugs)* - Jan 16 [P2, N=48; ORR was 35.6%; Median PFS and OS were 199 days and 677 days, respectively; P2 data]
- ⬇J&J withdraws breast-cancer test, citing low adoption *(WSJ)* - Jan 11 [J&J voluntarily withrew the Genesearch Breast Lymph-Node Assay from US and European markets due to low usage; Diagnostic test withdrawal]
- New breast screening limits face reversal *(WSJ)* - Jan 12 [Lawmakers approved an amendment to its health-overhaul bill that effectively nullified the new guidelines and promised mammogram coverage for women starting at age 40; Mammogram guidelines]
- Safety study in subjects with metastatic breast cancer who progressed after taxanes treatment. (GLICO-0801) *(Clinicaltrials.gov)* - Jan 14 [Grupo Latino Americano de Investigacoes Clinicas em Oncologia / P2, N=165; Recruiting; New P2 trial]

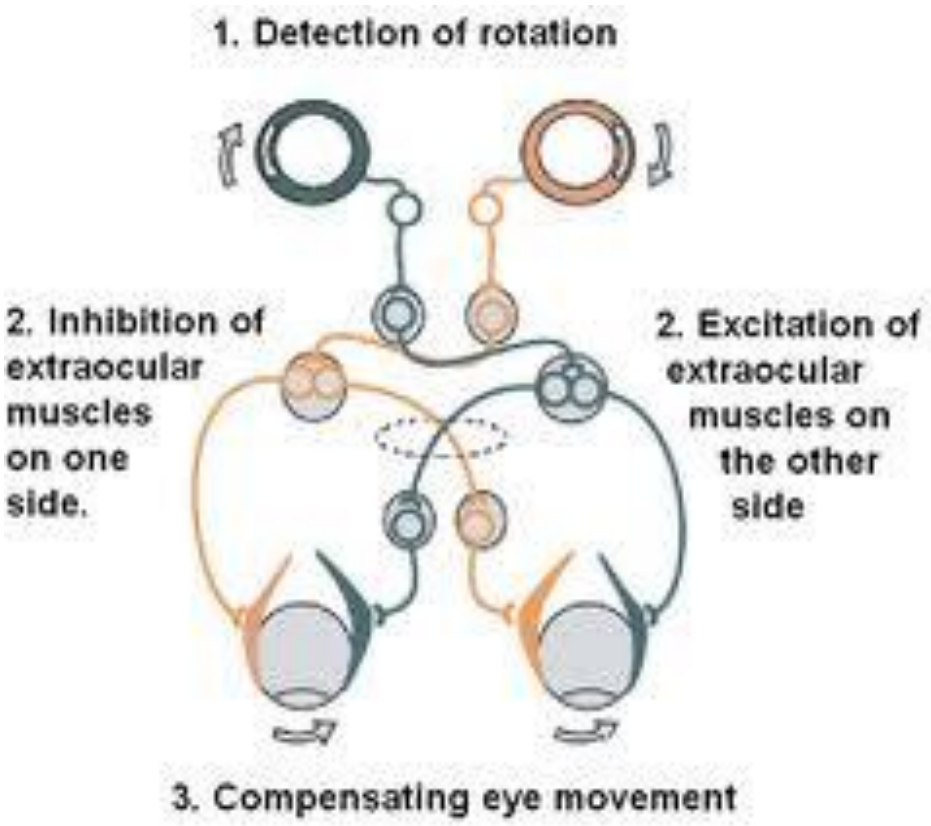
Initiatives

1. A virtual clinic

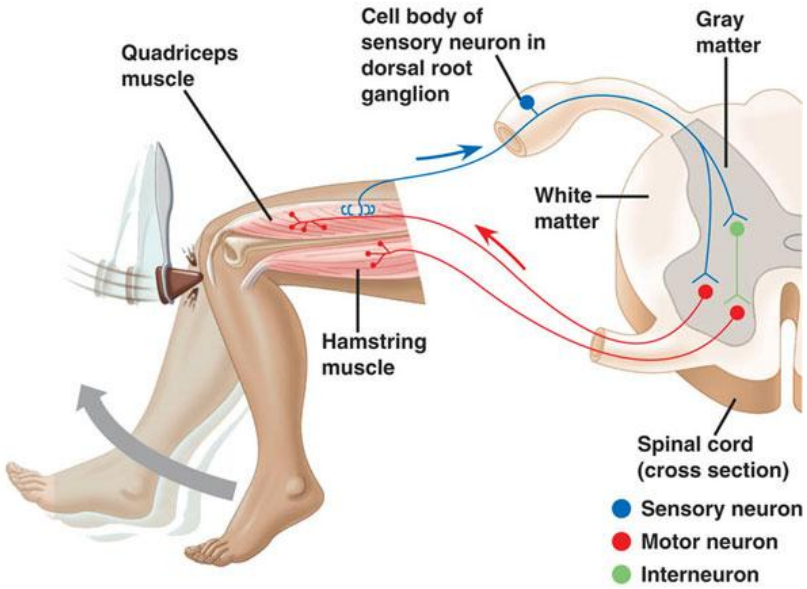
askmedicaldoctor.com
askdoctorforfree.com
onlineobesitydoctor.com
onlinediabetesdoctor.com
visitdoctoronline.com
askanoncologistnow.com
amipregnantornot.com
womenshealthdr.com

1. A system to verify treatment strategies (prescriptions)

Simple control systems

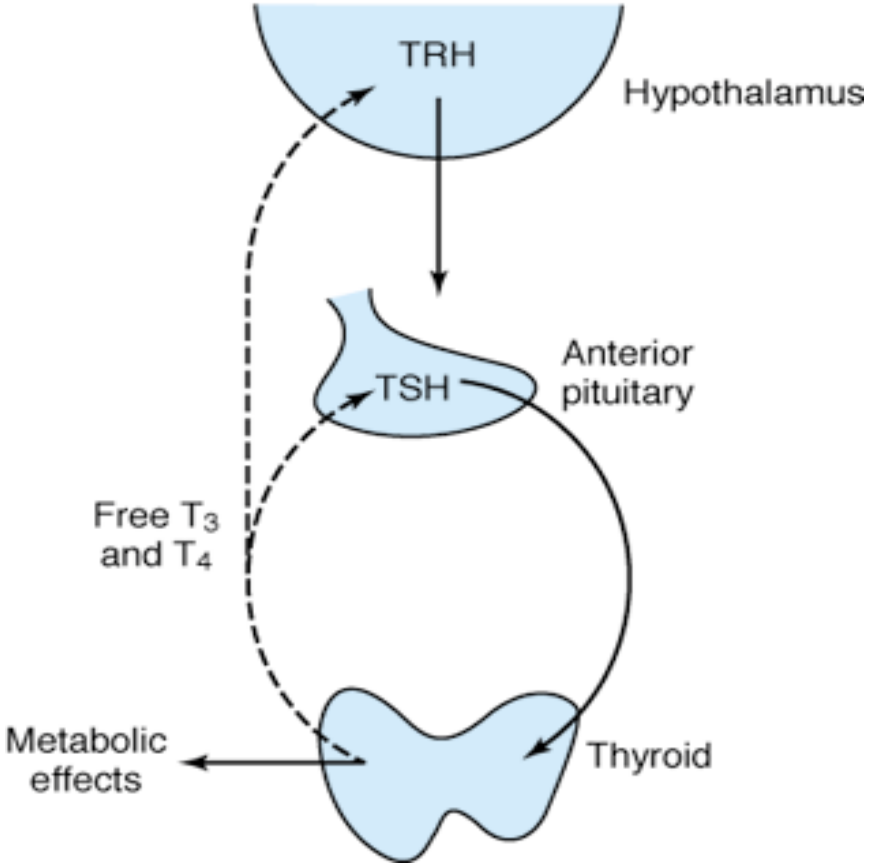


Vestibulo-ocular reflex



Stretch reflex of quadriceps femoris

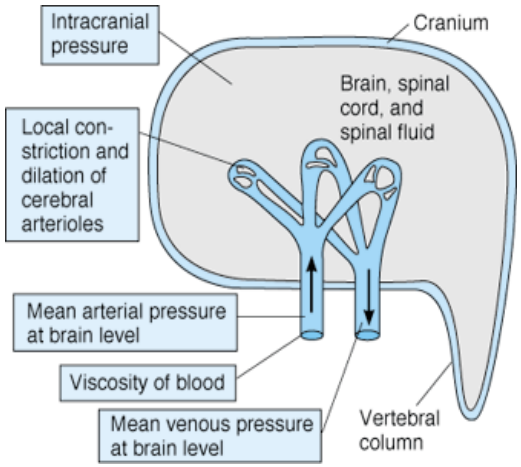
Endocrinology

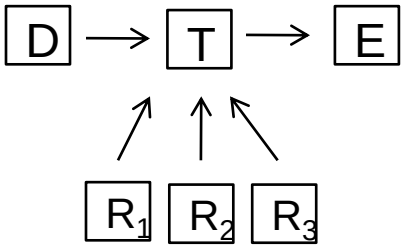


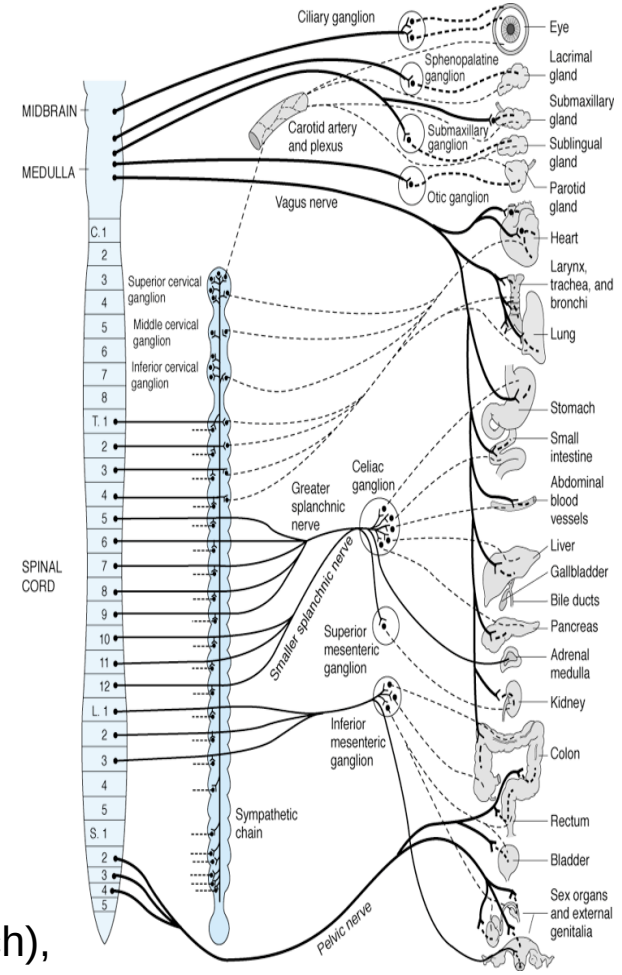
Autoregulation

The capacity of tissues to regulate their own blood flow is referred to as **autoregulation.**

In the **brain**, auto regulation maintains a normal cerebral blood flow at arterial pressures of 65-140 mm Hg







R1 (intrinsic contractile response of smooth muscle to stretch), R2 (stimulation of the vasomotor area) etc., are independent regulatory systems

TABLE 258-2 Stepwise Approach to Treatment of Elevated Intracranial Pressure[a]

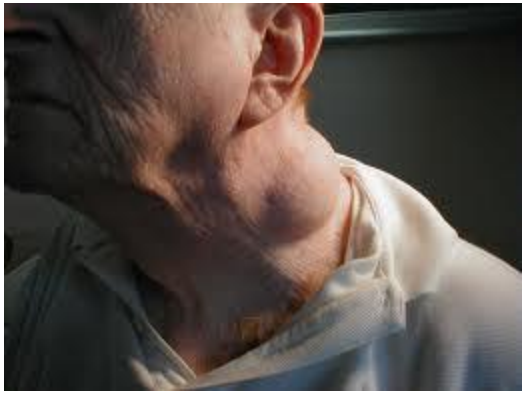
Insert ICP monitor—ventriculostomy versus parenchymal device
General goals: maintain ICP < 20 mmHg and CPP > 70 mmHg

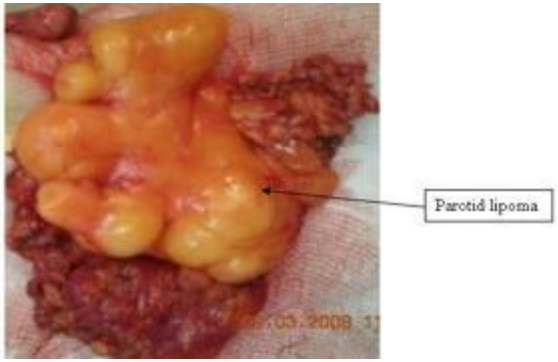
For ICP > 20–25 mmHg for >5 min:

1. Drain CSF via ventriculostomy (if in place)
2. Elevate head of the bed
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to Pa_{CO_2} 30–35 mmHg
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP > 70 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors)
8. Consider second-tier therapies for refractory elevated ICP
   a. High-dose barbiturate therapy ("pentobarb coma")
   b. Aggressive hyperventilation to Pa_{CO_2} < 30 mmHg
   c. Hemicraniectomy

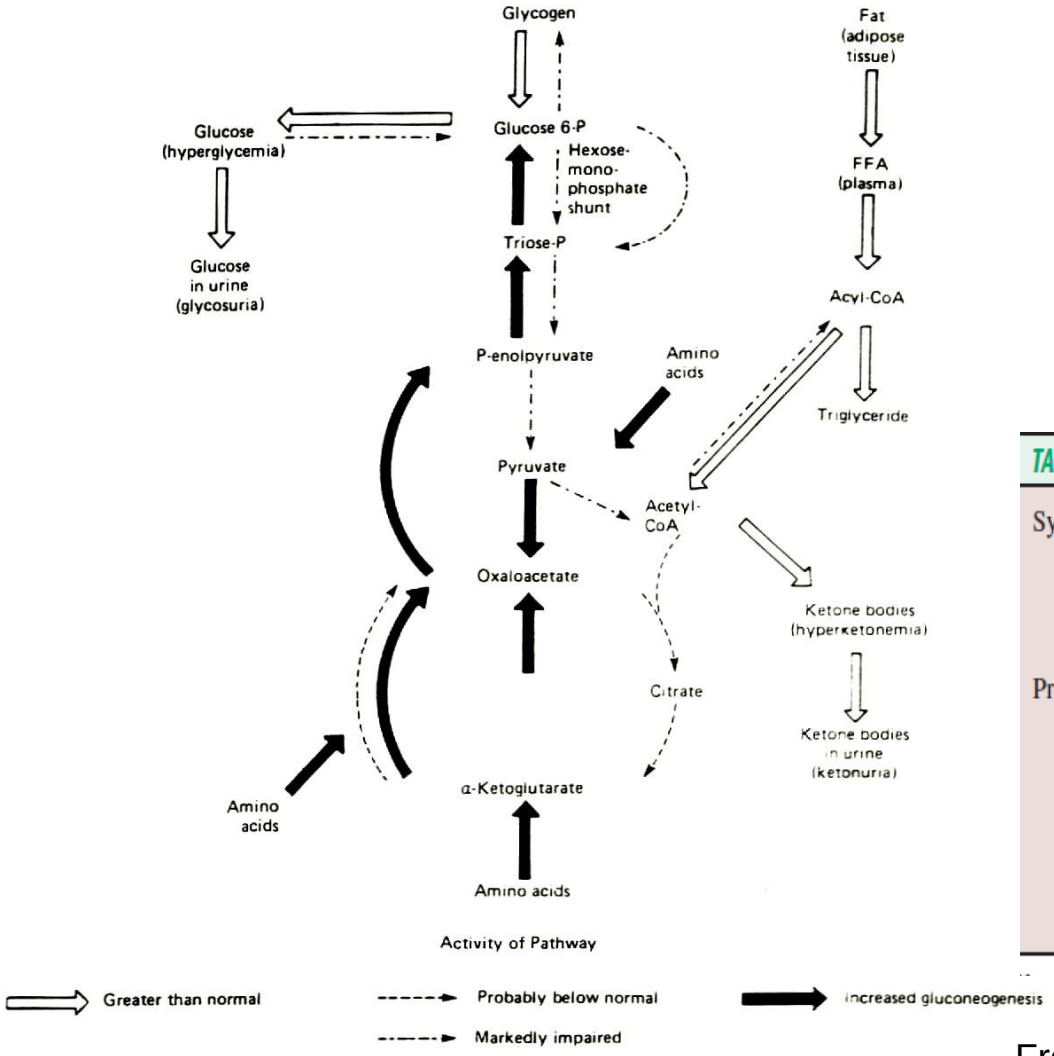
From, Harrison's Principles of Internal Medicine, 16th ed.

Lipoma - Excision





Diabetic ketoacidosis



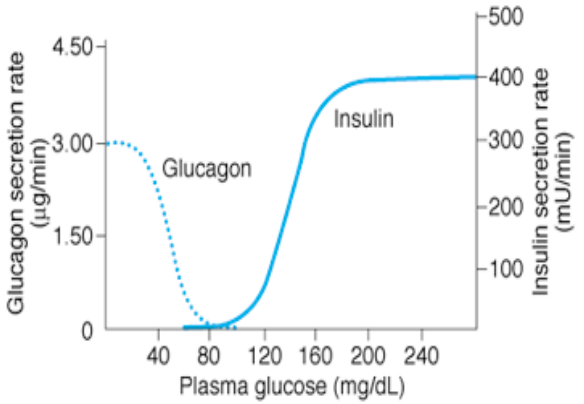
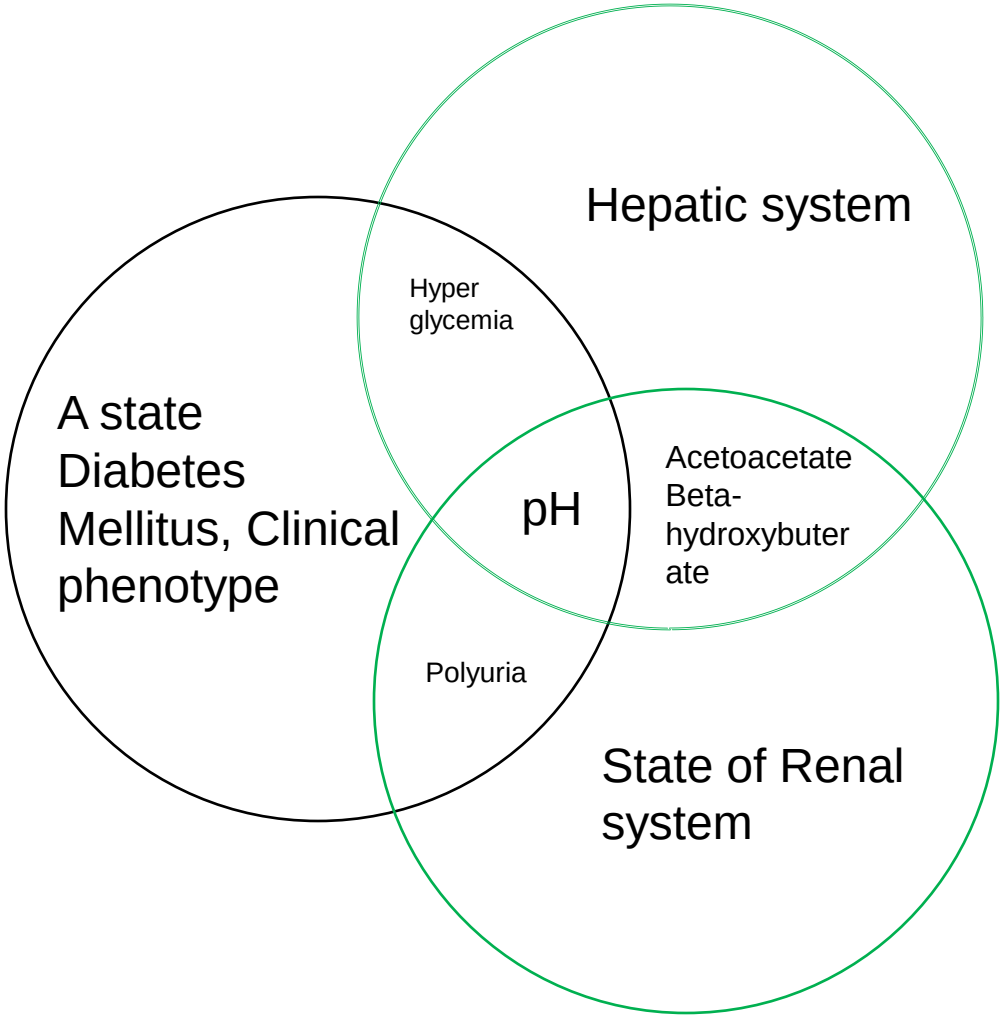


TABLE 323-5 Manifestations of Diabetic Ketoacidosis

Symptoms	Physical findings
Nausea/vomiting	Tachycardia
Thirst/polyuria	Dry mucous membranes/reduced skin turgor
Abdominal pain	Dehydration / hypotension
Shortness of breath	Tachypnea / Kussmaul respirations/respiratory distress
Precipitating events	Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
Inadequate insulin administration	Lethargy /obtundation / cerebral edema / possibly coma
Infection (pneumonia/UTI/ gastroenteritis/sepsis)	
Infarction (cerebral, coronary, mesenteric, peripheral)	
Drugs (cocaine)	
Pregnancy	

From, Review of Mecdical Physiology 21st ed.

Building arbitrary networks and kinematic graphs



Diabetic ketoacidosis

TABLE 323-6 Management of Diabetic Ketoacidosis

1. Confirm diagnosis (↑ plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH < 7.00 or unconscious.
3. Assess: Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate)
   Acid-base status—pH, HCO_3^-, P_{CO_2}, β-hydroxybutyrate
   Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (5–10 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/h; change to 5% glucose and 0.45% saline at 100–200 mL/h when plasma glucose reaches 250 mg/dL (14 mmol/L).
5. Administer regular insulin: IV (0.1 units/kg) or IM (0.4 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 10-fold if no response by 2–4 h. If initial serum potassium is < 3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected to > 3.3 mmol/L (3.3.meq/L).

From, Harrison's Principles of Internal Medicine, 16th ed.

Systemic Inflammatory Response Syndrome, MODS, MOF