I. CASE DESCRIPTION

A 29 year old male who works at your clinic believes he has diabetes mellitus. His father and paternal grandfather both developed this disease late in life. He has polyuria, polydypsia and polyphagia accompanied by weakness, weight loss and blurry vision. You test his urine and find 3+ glycosuria; blood glucose is 450 mg/dL. The patient does not want to take insulin and hopes that pills will be enough. On the other hand, he has heard that oral hypoglycemics can be bad for you.

II. DIABETES MELLITUS TYPE II

1. is characterized by insulin resistance and relative insulin deficiency
2. is associated with both hereditary and environmental factors
   → 40-50% increase in risk for individual with affected first degree relatives
   → significant association with obesity
3. if uncontrolled, may lead to such pathologies as diabetic retinopathy, autonomic neuropathy and nephropathy

III. NON-PHARMACOLOGIC INTERVENTIONS

1. Diet changes: Low calorie diet can reduce fasting glucose and increase insulin sensitivity in five days (hypothesized due to hepatic glycogenolysis).
   a) not effective over long term (three years in the United Kingdom Prospective Diabetes Study)
2. Exercise: Besides weight loss, produces increased insulin sensitivity and delays onset of overt diabetes.

IV. TREATMENT STRATEGIES WITH ORAL HYPOGLYCEMICS

[Diagram removed for copyright reasons.]

Inzucchi. (2002) JAMA 287 (3): 360-372.

A. Monitoring efficacy
1. Blood glucose concentrations
   a) measure mean blood glucose concentrations before meals and bedtime; mid morning and mid afternoon
   b) keep track of fluctuations over the day
   c) monitor day-to-day variations in mean glucose level
2. HbA1c
   a) average measurement indicates mean glucose level over the previous 6 to 8 weeks. Target is 7.0%
   b) potential for false values: falsely high if RBC turnover is lower than normal (eg., iron deficiency anemia) or low if turnover higher than normal (eg., hemolysis)

B. Classifying oral hypoglycemics

Approach	Class	Cost: 30 days of tx	▼ Fasting plasma glucose (mg/dL)	▼ HbA1c (%)	Lipid profile	Side effects
Improve insulin action	Biguanides -metformin	$70.43	50-70	1.5-2	Decrease TG, LDL Increase HDL	Weight loss GI events Lactic acidosis
	TZD's -rosiglitazone	$78.00	60-80	1.4-2.6	Increase HDL, LDL	Weight gain Fluid retention Lower Hb
Increase insulin secretion	Sulfonylureas -chlorpropamide -glipizide	$18.54 $10.45	60-70	0.8-2	None	Weight gain Hypoglycemia
	Meglitinides -ripaglinide	$27.80	65-75	0.5-2	None	Weight gain Hypoglycemia
Modulate carbohydrate absorption	α-glucosidase inhibitors -acarbose	$51.79	25-30	0.7-1.0	none	GI disturbances

http://www.endotext.org/diabetes/diabetes16/diabetes16.htm
Up-To-Date 2005

C. Pharmacokinetics

Class	Onset of effect within	Duration (hrs)	Time to observe significant change in HbA1c
Biguanides	days	More than 3-4 weeks	3 mo.
TZD's	12 weeks for max effect	"	6 mo.
Sulfonylureas -chlorpropamide -glipizide	6-8 hrs 1.5-2 hrs	24-72 14-16	3 mo.
Meglitinides	15-60 min.	Max 24	3 mo.
α-glucosidase inhibitors		4	3 mo.

Cheng AYY t al. (2005) CMAJ. 172 (2): 213-226
Up-to-Date 2005.

D. Structuring therapy?
1. Monotherapy: determined by tolerable side effect profile and expense
2. Most combinations of two oral hypoglycemics equally effective:
    a) using less than maximum doses, combination is more effective than monotherapy at reducing HbA1c
    b) certain combinations not recommended:
        i) SU+ another inducer of insulin secretion (risk of hypoglycemia)
3. Including insulin: when target of 7.0% HbA1c not reached
    a) Insulin + one oral hypoglycemic shown to be more effective than adding a third oral hypoglycemic drug to regimen
    b) Avoid certain combinations:
        i) Any inducer of insulin secretion + preprandial insulin (risk of hypoglycemia)
        ii) TZD + insulin (risk peripheral edema and heart failure)

V. INSULIN MONOTHERAPY
1. Side effects of weight gain and hypoglycemia may be more severe than combination therapy.
2. Necessary for patients with persistent hyperglycemia.