Alpha Adrenoceptor Antagonists
Beta Adrenoceptor Antagonists
Ganglion-Blocking Drugs

Alpha-Receptor Antagonist Drugs

Pharmacologic Effects

Cardiovascular Effects

- Decrease peripheral vascular resistance and blood pressure.
- Prevent the pressor effects of usual doses of α agonists
- Alpha-receptor antagonists often cause orthostatic hypotension and reflex tachycardia; nonselective (α 1 = α 2,) blockers cause tachycardia if blood pressure is lowered below normal.

- **Orthostatic hypotension** is due to blockade of α 1 receptors in vascular smooth muscle.
- Contraction of veins is an important component of the normal capacity to maintain blood pressure in the upright position since it decreases venous pooling in the periphery.
- Constriction of arterioles in the legs also contributes to the normal orthostatic response.
- **Tachycardia** is marked with agents that block α 2-presynaptic receptors in the heart, since the augmented release of NE will further stimulate β1 receptors in the heart.

Other Effects

- Blockade of α receptors in other tissues elicits **miosis** and nasal stuffiness.

- **Alpha1** receptors are expressed in the base of the bladder and the prostate, and their blockade decreases resistance to the flow of urine.
- Alpha blockers are used for the treatment of urinary retention due to prostatic hyperplasia .

Non selective alpha blockers

Phenoxybenzamine

Binds covalently to α receptors, causing irreversible blockade of long duration (14–48 h).

Blocks α1& to less extent α2 receptors.

Also inhibits reuptake of NE and blocks histamine (H1), ACh, and serotonin receptors.

Causes little fall in BP in normal supine individuals, it reduces BP when sympathetic tone is high, e.g., as a result of upright posture.

Absorbed poorly but usually given orally.

Uses: treatment of **pheochromocytoma,** Peripheral vascular diseases

Adverse effects

Orthostatic hypotension, tachycardia, Nasal stuffiness and inhibition of ejaculation.

Phentolamine

- Rapidly acting α blocker with short duration t½ 19 min.
- Competitive α1 and α2 antagonist.
- Reduces peripheral resistance (α1) and causes cardiac stimulation (α 2 receptors blockade enhances release of NE) .
- minor inhibitory effects at 5HT receptors and agonist effects at muscarinic (salivary, sweat, lacrimal) and H1 and H2 receptors (Increase acid secretion).
- Uses: Diagnostic of pheochromocytoma, control of hypertension due to clonidine withdrawal, Cheese reaction.
- To counteract vasoconstriction due to NE, Dopamine.
- **Adverse effects:** severe tachycardia, arrhythmias, and myocardial ischemia.

Selective alpha 1 blockers

Prazosin

- Highly selective α1 &1000-fold less potent at α 2 receptors.
- Relaxes **both arterial and venous vascular** smooth muscle & smooth muscle in the **prostate**, due to blockade of α 1 receptors with **no or little tachycardia**
- Extensively metabolized, only 50% is available after oral administration. The half-life is **3** hours. Favorable effect on plasma lipids: increase HDL/LDL ratio.
- **Uses** Antihypertensive ,Benign prostatic hyperplasia (BPH) Blocks α1 in bladder trigone & prostate & decreases tone & Improves urine flow .
- **Adverse effects**: First dose phenomenon i.e. postural hypotension with initial doses.

Terazosin

High bioavailability. The half-life is 9–12 hours.

Doxazosin

Has a longer half-life of about 22 hours.

Tamsulosin

Uroselective α1A/ α1D blocker. α 1A are predominant in bladder base & prostate.

30 times high affinity for α1A

High bioavailability and a half-life of 9–15 hours.

Has greater potency in inhibiting contraction in *prostate* smooth muscle versus *vascular* smooth muscle .

It is used to treat **BPH.**

No effect on BP and heart rate.

Side Effects: Dizziness & retrograde ejaculation.

Other Alpha- Adrenoceptor Antagonists

Labetalol

- Has both α1 and β-antagonistic effects

Chlorpromazine and **haloperidol**

- Potent dopamine receptor antagonists (Neuroleptic drugs) but are also antagonists at α receptors.

  Their antagonism of α receptors causes hypotension.

Ergot alkaloids

- **Ergotoxine**, **Ergotamine** are partial agonist and antagonist at adrenergic α, 5HT and DA receptors. Ergotoxine, dihydroergotoxine are more potent α blocker and less potent vasoconstrictor than ergotamine. USE: Ergotamine is used in Migraine

Yohimbine

- An indole alkaloid, is **α 2-selective antagonist**. Blocks other receptors also – 5HT, DA
- Increases ADH release
- Enhances sexual activity – aphrodisiac
- Sometimes used in the treatment of **orthostatic hypotension** because it promotes NE release through blockade of presynaptic α 2 receptors.
- Was widely used to improve male **erectile dysfunction** but has been superseded by phosphodiesterase-5 inhibitors like **sildenafil.**

Uses of the Alpha-Receptor–Blocking Drugs

1- Pheochromocytoma

Tumor of the adrenal medulla or sympathetic ganglion cells.

Causes intermittent or sustained hypertension, headaches, palpitations & increased sweating.

Phenoxybenzamine (orally) preoperative to control hypertension & for the **chronic treatment of inoperable or metastatic pheochromocytoma.**

Beta-receptor antagonists used to reverse the cardiac effects. Should not be used prior to establishing effective α -receptor blockade.

Metyrosine

α -methyltyrosine, a competitive inhibitor of tyrosine hydroxylase.

Used in inoperable or metastatic pheochromocytoma.

Can cause **extrapyramidal effects** due to reduced dopamine levels

2-Hypertensive Emergencies

Labetalol is used in **Hypertensive Emergencies**

3-Treatment of overdose of α1 agonis (phentolamine).

4-Chronic Hypertension

α 1-selective antagonists in mild to moderate systemic hypertension.

Not recommended as monotherapy because other drugs are more effective in preventing heart failure.

Their major adverse effect is orthostatic hypotension, which may be severe after the first few doses but is otherwise uncommon (First-Dose Phenomenon).

They may cause dizziness.

5-Peripheral Vascular Disease

Raynaud's phenomenon (excessive reversible vasospasm in the peripheral circulation). **Prazosin** or **phenoxybenzamine** are used but **calcium channel blockers** are preferable for most patients.

6-Urinary Obstruction

Benign prostatic hyperplasia (BPH) is common in elderly men.

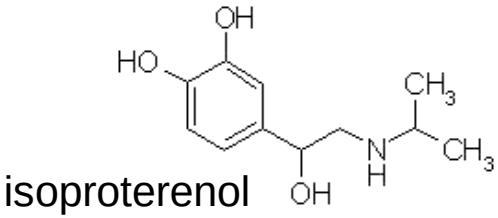
Improving urine flow involves partial reversal of smooth muscle contraction in the enlarged prostate and in the bladder base.

Prazosin, doxazosin, and terazosin are all effective.

Tamsulosin is **α 1A-receptor antagonists** effective in BPH and has relatively minor effects on blood pressure at a low dose & preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists.

β- Adrenoceptor Antagonists

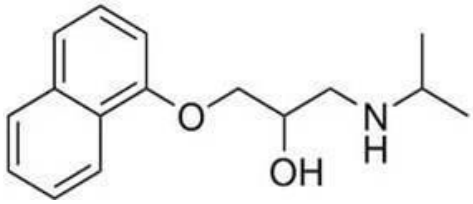
More specific effect on β receptors due to similarity to isoproterenol structure.



isoproterenol

Differ in their relative affinities for β 1 and β 2 receptors.

propranolol



The **selectivity is dose-related; it tends to diminish at higher drug concentrations.**

Other major differences relate to their pharmacokinetic characteristics and **local anesthetic (membrane-stabilizing)** effects. However, the concentration in plasma is **too low** for the anesthetic effects.

Most drugs are well absorbed after oral administration; peak concentrations **1–3** hours after ingestion.

	Selectivity	Partial Agonist	Local Anesthetic	t½
Acebutolol	β1	Yes	**Yes**	3–4hours
Atenolol	β1	No	No	6–9 hours
Bisoprolol	β1	No	No	9–12 hours
Esmolol	β1	No	No	10 minutes
Metoprolol	β 1	No	**Yes**	3–4 hours
Nadolol	None	No	No	14–24 hours
Penbutolol	None	Yes	No	5 hours
Pindolol	None	Yes	**Yes**	3–4 hours
Propranolol	None	No	**Yes**	3.5–6 hours
Sotalol	None	No	No	12 hours
Timolol	None	No	No	4–5 hours
Labetalol	None (α blocker)	Yes	**Yes**	5 hours

Distribution and Clearance

Rapidly distributed with large volumes of distribution.

Propranolol & **penbutolol** are lipophilic and readily cross the blood-brain barrier .

Most β antagonists have half-lives of 3–10 hours.

Esmolol is rapidly hydrolyzed & its half-life 10 minute.

Propranolol and **metoprolol** are extensively metabolized in the liver.

Atenolol & **pindolol** are less completely metabolized.

Nadolol is excreted unchanged in the urine and has the longest half-life (up to 24 hours).

The half-life of **Nadolol** is prolonged in renal failure.

The effects of these drugs are well beyond the time predicted from half-life data.

Pharmacodynamics

Effects on the Cardiovascular System

Very valuable in **hypertension, angina** and **chronic heart failure** and **following myocardial infarction (MI)**.

Heart: ↓ HR, ↓ stroke volume, ↓ COP. Slowed AV conduction.

↓cardiac work and oxygen consumption.

Blood vessels: fall in BP both diastolic and systolic after continuous treatment.

Do not cause hypotension in healthy individuals with normal BP

In the vascular system, β -receptor blockade **opposes β 2-mediated vasodilation**.

This may leads to a **rise in peripheral resistance** from **unopposed α -receptor-mediated effects** as the sympathetic nervous system is activated in response to the fall in cardiac output, but **chronic administration leads to a fall in peripheral resistance in patients with hypertension.**

Nonselective and β 1-blocking drugs antagonize the release of **renin** caused by the sympathetic nervous system.

Effects on the Respiratory Tract

Increase in airway resistance, particularly in patients with asthma.

β1 blockers are safer than nonselective β blockers.

β 1-selective blocker are not sufficiently specific to *completely* avoid interactions with β 2 receptors.

Consequently, these drugs should generally be **avoided in patients with asthma**.

Many patients with chronic obstructive pulmonary disease may tolerate these drugs & the benefits e.g. in patients with concomitant **ischemic heart disease**, may outweigh the risks.

Effects on the Eye

Reduce intraocular pressure in **glaucoma** by decreasing aqueous humor production.

Glaucoma is treated by:

1- reduction of aqueous humor secretion.

2- enhancement of aqueous out-flow.

Drugs useful in reducing intraocular pressure:

Cholinomimetics, α agonists, β blockers

prostaglandin F2 analogs., diuretics

Prostaglandin analogs & β blockers are the most popular.

Metabolic and Endocrine Effects

- Beta-receptor antagonists increases LDL, triglycerides, ↓ HDL by inhibiting **lipolysis.**
- **Glycogenolysis** in the liver is inhibited after β 2-receptor blockade.
- β –blockers should be used with caution in **insulin-dependent diabetic patients**.

  β blockers delay recovery from hypoglycemia due to insulin and oral anti diabetics and mask early symptoms of hypoglycemia (tremors, sweating & tachycardia).

Effects Not Related to Beta-Blockade

Partial agonists Pindolol & **Penbutolol** are **useful** in patients who develop **bradycardia or bronchoconstriction.**

Sotalol is a nonselective β blocker that has **marked class III antiarrhythmic** effects, reflecting **potassium channel blockade** (used to treat both ventricular & supraventricular arrhythmias).

Local anesthetic action (**membrane-stabilizing**)

is a prominent effect of several β blockers (Propranolol, Pindolol, Labetalol, Metoprolol, Acebutolol).

However, the concentration in plasma is **too low** for the anesthetic effects to be evident.

These membrane-stabilizing β- blockers are **not used topically on the eye,** where local anesthesia of the cornea would be undesirable.

Specific Agents

Propranolol

- Prototype of β -blocking drug.
- Has low and dose-dependent bioavailability (first-pass metabolism).
- First-pass effect varies among individuals, so there is great individual variability in the plasma concentrations after oral propranolol.
- A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period.
- No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear.
- It has no partial agonist action at β receptors.

Other non-selective beta blockers

Nadolol

Has a **very long duration of action**.

Its spectrum of action is similar to that of timolol.

Timolol

Nonselective with no local anesthetic activity used topically to treat glaucoma.

Sotalol

Nonselective that also exhibits Class III antiarrhythmic properties.

Cardioselective β Blockers (**β1-selective** antagonists)

less effects on bronchioles, carbohydrate metabolism, lipids.

Lower incidences of Cold hands and feet.

Less liable to impair exercise tolerance

Safer in patients who experience bronchoconstriction in response to propranolol, but their β 1 selectivity is modest, so they should be used with great caution in patients with **asthma.**

β1-selective antagonists cont..

- However, the benefits may exceed the risks, e.g., in patients with myocardial infarction.
- Beta1-selective antagonists are preferred in patients with **diabetes or peripheral vascular disease** since β 2 receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).

Metoprolol

- Cardioselective, Preferred in diabetics on insulin or oral hypoglycemics.
- Less likely to worsen asthma.
- used to treat **angina** and **hypertension** & also used to treat or prevent Myocardial Infarction (AMI) without bradycardia.

Atenolol

- Selective beta 1 blocker with low lipid solubility. Longer duration action. One dose/day.
- Side effects related to CNS are less prominent No effect on bronchus, carbohydrate metabolism, lipids
- Most commonly used in Hypertension & angina .

Nebivolol

The most highly selective β 1 blocker.

↑ endothelial NO release (vasodilating effect)

Antioxidant properties that can protect the vascular wall from free radicals that damage blood vessels and thereby contribute to the progression of cardiovascular disease.

Bisoprolol

Selective beta 1 blocker with low lipid solubility. Longer duration action. One dose/day

used to treat cardiovascular diseases such as hypertension, coronary heart disease, arrhythmias.

Esmolol

- Ultra-short–acting β 1-selective blocker.
- Contains an ester linkage; esterases in red blood cells rapidly metabolize it.
- Has a short half-life (about 10 minutes). During continuous infusions of esmolol, **steady-state concentrations** are achieved quickly, and actions of the drug are terminated rapidly when its infusion is discontinued.
- Esmolol may be **safer** in critically ill patients who require a β -adrenoceptor antagonist.
- Esmolol is useful in controlling **supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis, perioperative hypertension, and myocardial ischemia in acutely ill patients**.

β Blockers with **partial β-agonist activity.**

Effective in hypertension and angina & less likely to cause **bronchoconstriction, bradycardia and abnormalities in plasma lipids** than other β blockers.

Pindolol is a non-selective beta- adrenoceptor/5-HT1A antagonist accelerates the antidepressant effect of selective serotonin reuptake inhibitors.

Celiprolol is a β 1-selective antagonist with a **partial β2 -agonist activity** & may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation.

Acebutolol is also a β 1-selective antagonist.

Drugs that block both alpha and beta receptors

Labetalol

- Racemic mixture of two pairs of isomers .
- The (*S*,*S*) & (*R*,*S*) isomers are inactive.
- (*S*,*R*)- is a potent α1 blocker
- (*R*,*R*)-isomer is a potent β blocker.
- Causes Hypotension with less tachycardia than occurs with phentolamine & similar α blockers. it is a **partial agonist** at beta2- receptors

Carvedilol

- A nonselective beta blocker/alpha-1 blocker, calcium channel blocker. More potent at β than at α1 receptors
- Antioxidant property.
- Use: Hypertension, Angina, congestive heart failure

Clinical Uses of the Beta-Receptor–Blockers.

Hypertension

- Although many hypertensive patients respond to a β blocker used alone, the drug is often used with either a diuretic or a vasodilator.
- In spite of the short half-life of many β antagonists, these drugs **may be administered once or twice daily** and still have an adequate therapeutic effect.
- May be less effective in the **elderly** and in individuals of **African ancestry**. However, these differences are relatively small and may not apply to an individual patient.

Ischemic Heart Disease

Clinical Uses cont..

- Reduce the frequency of anginal episodes and improve exercise tolerance in patients with angina.
- Decrease cardiac work & reduce oxygen demand.
- Slow heart rate may contribute to clinical benefits.
- The long-term use of **timolol, propranolol,** or **metoprolol** in patients who have had a myocardial infarction prolongs survival
- β blockers are strongly indicated in the acute phase of a myocardial infarction.
- Contraindications include bradycardia, hypotension, moderate or severe left ventricular failure, shock, heart block, and active airways disease.

Cardiac Arrhythmias

Clinical Uses cont..

- Effective in the treatment of both supraventricular and ventricular arrhythmias
- By increasing the **AV nodal refractory** period,

  β antagonists slow ventricular response rates in atrial **flutter and fibrillation**.
- They **reduce ventricular ectopic** beats, particularly if caused by catecholamines.

- **Sotalo**l has a **marked class III antiarrhythmic** effects, due to **potassium channel blockade** (treats both ventricular & supraventricular arrhythmias).

Heart Failure

Clinical Uses cont..

- Clinical trials have demonstrated that at least three β antagonists, **metoprolol, bisoprolol,** and **carvedilol** are effective in reducing mortality in selected patients with chronic heart failure.
- Although administration of these drugs may worsen acute congestive heart failure, cautious long-term use with gradual dose increments in patients who tolerate them may prolong life.
- Although mechanisms are uncertain, there appear to be beneficial effects on **myocardial remodeling** and in decreasing the risk of sudden death.

Glaucoma

- Systemic administration of β -blocking drugs for other indications, reduced intraocular pressure in patients with glaucoma. Topical administration also reduces intraocular pressure.
- The mechanism involves reduced production of aqueous humor by the ciliary body.
- **Timolol** and related β antagonists are suitable for local use in the eye because they lack local anesthetic properties.
- Beta antagonists have an efficacy comparable to that of **epinephrine** or **pilocarpine** in open-angle glaucoma and are far better tolerated.
- Sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart and airways in susceptible individuals.

Hyperthyroidism

- Excessive CA action is important in the pathophysiology of hyperthyroidism, especially in relation to the heart
- The β antagonists are beneficial in this condition due to **blockade of adrenoceptors & in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.**
- Propranolol has been used extensively in patients with **thyroid storm** (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.

Neurologic Diseases

- Propranolol reduces the frequency and intensity of **migraine** headache.
- Other β -receptor antagonists with preventive efficacy include **metoprolol** , **atenolol, timolol,** and **nadolol**.
- The mechanism is not known.
- β antagonists reduce certain **tremors.**
- The **somatic manifestations of anxiety** may respond dramatically to low doses of **propranolol**, particularly when taken prophylactically.
- Benefit has been found in musicians with **performance anxiety ("stage fright").**
- Propranolol may be used in symptomatic treatment of alcohol withdrawal in some patients.

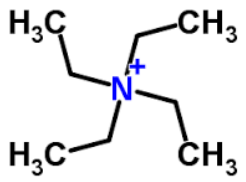
Clinical Toxicity of the Beta-Receptor Antagonist Drugs

- **Bradycardia** is the most common adverse effect. Coolness of hands and feet in winter.
- CNS effects include mild sedation, vivid dreams, and rarely, depression.
- Nonselective agents commonly causes worsening of preexisting **asthma.**
- Caution is required in patients with severe peripheral vascular disease and in patients with compensated heart failure even though long-term use may prolong life.
- A very small dose of a β antagonist may provoke severe cardiac failure in a susceptible individual.

- Beta blockers may interact with the calcium antagonist **verapamil** causing bradycardia, heart failure, and cardiac conduction abnormalities. These adverse effects may even arise in susceptible patients taking a **topical** β blocker and oral verapamil.
- Patients with ischemic heart disease or hypertension may be at increased risk if β blockade is suddenly interrupted.
- This might involve **up-regulation** of **β receptors**.
- It is inadvisable to use β antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions. **Beta1-selective antagonists** are safer in these patients

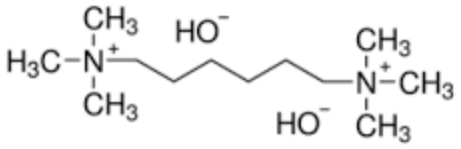
Ganglion-Blocking Drugs

Tetraethylammonium (TEA)



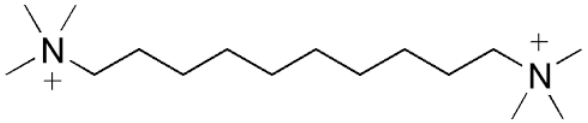
First ganglion blocker, very short duration of action.

Hexamethonium ("C6")

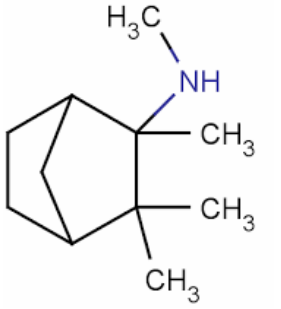


The first drug effective for hypertension.

Decamethonium, "C10" analog of hexamethonium, is a depolarizing neuromuscular blocker.

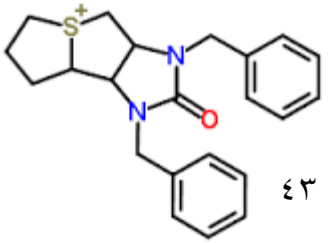


Mecamylamine



A secondary amine, developed to improve absorption from the GIT because the quaternary amine were poorly absorbed after oral administration.

Trimethaphan



A short-acting ganglion blocker, is inactive orally & is given by intravenous infusion.

Mechanism of Action

- Ganglionic nicotinic receptors are subject to both depolarizing and nondepolarizing blockade
- Nicotine & acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.
- Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists.
- However, **hexamethonium** actually produces most of its blockade by occupying sites in or on the nicotinic ion channel, not by occupying the cholinoceptor itself.
- **Trimethaphan** blocks the nicotinic receptor, not the channel pore.
- Blockade can be reversed by increasing the concentration of an agonist, e.g., acetylcholine.

Organ System Effects

Central Nervous System

Mecamylamine enters the CNS causing Sedation, tremor, **choreiform** movements, and mental abnormalities.

Eye

- **Cycloplegia** with loss of accommodation & **moderate dilation of the pupil** because parasympathetic tone usually dominates this tissue.

Cardiovascular System

- Marked decrease in arteriolar and venomotor tone.
- **BP** may fall because both peripheral vascular resistance and venous return are decreased
- **Orthostatic or postural hypotension**, **diminished contractility** and, because the sinoatrial node is usually dominated by the parasympathetic nervous system, a **moderate tachycardia**.

GIT

- Secretion & Motility are profoundly inhibited, and constipation can be marked.

Other Systems

- Hesitancy in urination and may precipitate urinary retention in men with prostatic hyperplasia.
- **Sexual function** is impaired in that both erection and ejaculation.
- **Sweating** is reduced by the ganglion-blocking drugs.

Response to Autonomic Drugs

- Patients receiving ganglion-blocking drugs are fully responsive to drugs acting on muscarinic, alpha , and beta adrenergic receptors.
- Responses may be exaggerated or even reversed (e.g., IV administered **NE** may cause tachycardia rather than bradycardia), because homeostatic reflexes are absent.

Clinical Applications & Toxicity

- Ganglion blockers are **used infrequently** because more selective agents are available.

Mecamylamine

- Blocks central nicotinic receptors and has been advocated as a possible adjunct with the transdermal nicotine patch to **reduce nicotine craving in patients attempting to quit smoking**.

Trimethaphan

- Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery to reduce bleeding in the operative field.

- The toxicity of the ganglion-blocking drugs is limited to the autonomic effects.
- These effects are intolerable except for acute use.

The Hexamethonium Man

W. D. M. Paton, Pharm. Rev. 6, 59 (1954)

- He is a pink complexioned person, except when he has stood for a long time, when he may get pale and faint.
- His handshake is warm and dry. He is a placid and relaxed companion; for instance he may laugh, but he can't cry because the tears cannot come.
- Your rudest story will not make him blush, and the most unpleasant circumstances will fail to make him pale.
- His socks and his collars stay very clean & sweet.

- He wears corsets and may, if you meet him out, be rather fidgety (corsets to compress his splanchnic vascular pool, fidgety to keep the venous return going from his legs).
- He dislikes speaking much unless helped with something to moisten his dry mouth and throat.
- He is long-sighted and easily blinded by bright light.
- The redness of his eyeballs may suggest irregular habits and in fact his head is rather weak. But he always behaves like a gentleman and never belches or hiccups.
- He tends to get cold and keeps well wrapped up. But his health is good; he does not have chilblains and those diseases of modern civilization, hypertension and peptic ulcers, pass him by.

- He is thin because his appetite is modest; he never feels hunger pains and his stomach never rumbles.
- He gets rather constipated so his intake of liquid paraffin is high.
- As old age comes on he will suffer from retention of urine and impotence, but frequency, percipitancy (must hurry), and strangury (frequent urination of small volumes that are expelled slowly only by straining and despite a severe sense of urgency) will not worry him.
- One is uncertain how he will end, but perhaps if he is not careful, by eating less and less and getting colder and colder, he will sink into a symptomless, hypoglycemic coma and die, as was proposed for the universe, a sort of entropy death.