

ON THE BEAT

Appreciation

Ancel Keys, Ph.D., the physiologist who became a leading authority on the role of diet in health, died on November 20 at the age of 100. His influence stretched from the skies of World War II, owing to his role in developing "K-rations" for U.S. paratroopers, to the cover of Time magazine, for his role in the discovery and popularization of the link between cholesterol and heart disease.

Dr. Keys attended the University of California, Berkeley, where he received a B.A. in economics, an M.S. in biology, and a Ph.D. in oceanography and biology. He received a second Ph.D., in physiology, from King's College, Cambridge in 1938.

Dr. Keys became a professor at the University of Minnesota in 1936, and organized what would become the Laboratory of Physiological Hygiene. He remained its director until his retirement in 1972.

Nicknamed "Mr. Cholesterol," Dr. Keys was most noted for his "Seven Countries Study," in which he postulated that the disparity in heart attack rates between nations was due to the influence of fat in the diets.

Finns, with the highest national heart attack, ate large quantities of animal fat and had high cholesterol levels. Cretans, with the lowest heart attack rate, ate far less fat, with olive oil the primary source, and had lower cholesterol levels. This was the first linkage between diet and coronary disease.

Such data led Dr. Keys to the development and popularization of the "Mediterranean Diet" in a series of best-selling books cowritten with his wife, Margaret Harvey, a biochemist.

Changes

Gary S. Roubin, M.D., was chosen head of the Department of Interventional Cardiology at Lenox Hill Hospital, New York. Dr. Roubin, the coinventor of the Gianturo-Roubin Flex-Stent, the first Food and Drug Administration-approved coronary artery stent, is slated to expand the new department in depth and breadth of service. This includes hiring Howard Cohen, M.D., formerly of the University of Pittsburgh, to serve as director of the heart failure and structural heart program, and Kirk Garratt, M.D., from the Mayo Clinic, who will serve as director of interventional cardiology research. Dr. Roubin returns to Lenox Hill Hospital where he was director of endovascular therapy in 1997-2003. Roubin's new team follows the departure of nine interventional cardiologists, including Jeffery Moses, M.D., former chief of interventional cardiology, who all left Lenox Hill

for Columbia University in August 2004.

The Cardiovascular Research Foundation will collaborate with Columbia University Medical Center (CUMC), New York, to translate basic science into new therapies and less invasive procedures for patients with cardiovascular disease. CUMC has also created a new Center for Interventional Vascular Therapy to foster collaboration across medical subspecialties.

The Heart Rhythm Society has relocated its headquarters to Washington from Nat-

ick, Mass. "Being in Washington will help us forge stronger alliances with governing agencies and health care groups whose work complements ours," said Stephen C. Hammill, M.D., president of the society.

Rx Briefs

The FDA issued a Class 1 recall on automated external defibrillators (AEDs) produced by the now-defunct Access CardioSystems Inc., warning customers to stop using them immediately. These devices are used by hospitals, fire departments, and emergency personnel. The AEDs were recalled because they may fail to deliver a shock due to a faulty circuit

board and/or may turn on unexpectedly due to a faulty switch and fail to operate.

The ASCOT trial of Pfizer's amlodipine (Norvasc) and perindopril (Coversyl) ended early because the drugs performed so well it would have been unethical to continue, said Peter Sever, Ph.D., of Imperial College, London, cochair of the 19,000-patient study. Patients on amlodipine (calcium channel blocker) and perindopril (ACE inhibitor) had substantially fewer cardiovascular events, including heart attacks, than did those on β -blockers and diuretics.

—Mark S. Lesney



BRIEF SUMMARY: For full Prescribing Information, see package insert.

INDICATIONS AND USAGE Hypertension: TOPROL-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. **Angina Pectoris:** TOPROL-XL is indicated in the long-term treatment of angina pectoris. **Heart Failure:** TOPROL-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, TOPROL-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure. **CONTRAINDICATIONS** TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS) and in patients who are hypersensitive to any component of this product.

WARNINGS

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TOPROL-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TOPROL-XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta₁-selectivity, however, TOPROL-XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁-selectivity is not absolute, a beta₂-stimulating agent should be administered concomitantly, and the lowest possible dose of TOPROL-XL should be used (see DOSAGE AND ADMINISTRATION). **Major Surgery:** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. TOPROL-XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers. **Diabetes and Hypoglycemia:** TOPROL-XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. **Thyrotoxicosis:** Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm. **Peripheral Vascular Disease:** Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals. **Calcium Channel Blockers:** Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

PRECAUTIONS General: TOPROL-XL should be used with caution in patients with impaired hepatic function. In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent. Worsening cardiac failure may occur during up-titration of TOPROL-XL. If such symptoms occur, diuretics should be increased and the dose of TOPROL-XL should not be advanced until clinical stability is restored (see DOSAGE AND ADMINISTRATION). It may be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of TOPROL-XL. **Information for Patients:** Patients should be advised to take TOPROL-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue TOPROL-XL without consulting the physician. Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with TOPROL-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking TOPROL-XL. Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath. **Laboratory Tests:** Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase. **Drug Interactions:** Catecholamine-depleting drugs (eg, reserpine, mono amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with TOPROL-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol. Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be followed for several days after clonidine administration has stopped. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats

at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor. All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella/mammalian-microsome* mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella/mammalian-microsome* mutagenicity test) were negative. No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient.

Pregnancy Category C: Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when TOPROL-XL is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Clinical studies of TOPROL-XL in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients. Of the 1,990 patients with heart failure randomized to TOPROL-XL in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse events between older and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Risk of Anaphylactic Reactions:** While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more



reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS Hypertension and Angina: Most adverse effects have been mild and transient. The following adverse reactions have been reported for immediate release metoprolol tartrate. **Central Nervous System:** Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported. **Cardiovascular:** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see WARNINGS). **Gastrointestinal:** Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients. **Hypersensitive Reactions:** Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported. **Miscellaneous:** Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus has also been reported. There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol. **Potential Adverse Reactions:** A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to TOPROL-XL. **Central Nervous System:** Reversible mental depression progressing to cataplexy; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. **Cardiovascular:** Intensification of AV block (see CONTRAINDICATIONS). **Hematologic:** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. **Hypersensitive Reactions:** Fever combined with aching and sore throat, laryngospasm, and respiratory distress. **Heart Failure:** In the MERIT-HF study, serious adverse events and adverse events leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing TOPROL-XL in daily doses up to 200 mg (mean dose 159 mg once-daily) (n=1990) to placebo (n=2001), 10.3% of TOPROL-XL patients discontinued for adverse events vs. 12.2% of placebo patients. The table

below lists adverse events in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the TOPROL-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Events Occurring in the MERIT-HF Study at an Incidence \geq 1% in the TOPROL-XL Group and Greater Than Placebo by More Than 0.5%

| | TOPROL-XL | Placebo |
|------------------------|-------------------------|-------------------------|
| | N=1990 % of patients | N=2001 % of patients |
| Dizziness/vertigo | 1.8 | 1.0 |
| Bradycardia | 1.5 | 0.4 |
| Accident and/or injury | 1.4 | 0.8 |

Other adverse events with an incidence of \geq 1% on TOPROL-XL and as common on placebo (within 0.5%) included myocardial infarction, pneumonia, cerebrovascular disorder, chest pain, dyspnea/dyspnea aggravated, syncope, coronary artery disorder, ventricular tachycardia/arrhythmia aggravated, hypotension, diabetes mellitus/diabetes mellitus aggravated, abdominal pain, and fatigue. **Post-Marketing Experience:** The following adverse reactions have been reported with TOPROL-XL in worldwide post-marketing use, regardless of causality: **Cardiovascular:** 2nd and 3rd degree heart block; **Gastrointestinal:** hepatitis, vomiting; **Hematologic:** thrombocytopenia; **Musculoskeletal:** arthralgia; **Nervous System/Psychiatric:** anxiety/nervousness, hallucinations, paresthesia; **Reproductive, male:** impotence; **Skin:** increased sweating, photosensitivity; **Special Sense Organs:** taste disturbances.

OVERDOSAGE Acute Toxicity: There have been a few reports of overdosage with TOPROL-XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since TOPROL-XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to TOPROL-XL. **Signs and Symptoms:** Overdosage of TOPROL-XL may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting, and cyanosis. **Treatment:** In general, patients with acute or recent myocardial infarction or congestive heart failure may be more hemodynamically unstable than other patients and should be treated accordingly. When possible the patient should be treated under intensive care conditions. On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed: **Elimination of the Drug:** Gastric lavage should be performed. **Bradycardia:** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously. **Hypotension:** A vasopressor should be administered, eg, levaterenol or dopamine. **Bronchospasm:** A beta₂-stimulating agent and/or a theophylline derivative should be administered. **Cardiac Failure:** A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be more considered.

DOSAGE AND ADMINISTRATION TOPROL-XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to TOPROL-XL, the same total daily dose of TOPROL-XL should be used. As with immediate release metoprolol, dosages of TOPROL-XL should be individualized and titration may be needed in some patients. TOPROL-XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed. **Hypertension:** The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied. **Angina Pectoris:** The dosage of TOPROL-XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until an optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS). **Heart Failure:** Dosage must be individualized and closely monitored during up-titration. Prior to initiation of TOPROL-XL, the dosing of diuretics, ACE inhibitors, and digitalis (if used) should be stabilized. The recommended starting dose of TOPROL-XL is 25 mg once daily for two weeks in patients with NYHA class II heart failure and 12.5 mg once daily in patients with more severe heart failure. The dose should then be doubled every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of TOPROL-XL. If transient worsening of heart failure occurs, it may be treated with increased doses of diuretics, and it may also be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. The dose of TOPROL-XL should not be increased until symptoms of worsening heart failure have been stabilized. Initial difficulty with titration should not preclude later attempts to introduce TOPROL-XL. If heart failure patients experience symptomatic bradycardia, the dose of TOPROL-XL should be reduced.

HOW SUPPLIED Tablets containing metoprolol succinate equivalent to the indicated weight of metoprolol tartrate, USP, are white, biconvex, film-coated, and scored.

| Tablet | Shape | Engraving | Bottle of 100 NDC 0186- | Unit Dose Packages of 100 NDC 0186- |
|--------|-------|-----------|-------------------------|-------------------------------------|
| 25 mg* | Oval | β | 1088-05 | 1088-39 |
| 50 mg | Round | A mo | 1090-05 | 1090-39 |
| 100 mg | Round | A ms | 1092-05 | 1092-39 |
| 200 mg | Oval | A my | 1094-05 | N/A |

*The 25 mg tablet is scored on both sides. Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature.)

All trademarks are the property of the AstraZeneca group © AstraZeneca 2002

Manufactured for: AstraZeneca LP
Wilmington, DE 19850
By: AstraZeneca AB
S-151 85 Södertälje, Sweden

Made in Sweden
64200-00
Rev. 11/02



INDEX OF ADVERTISERS

| | |
|---|---------|
| AstraZeneca LP. | |
| Toprol XL | 23-24 |
| Baxter Healthcare Corporation | |
| Brevibloc | 9-10 |
| Pfizer Inc. | |
| Inspira | 3-6 |
| Caduet | 13 |
| Roche Diagnostics | |
| Elecsys | 11 |
| Wyeth Pharmaceuticals Inc. and Monarch Pharmaceuticals, Inc. | |
| Altace | 20a-20b |