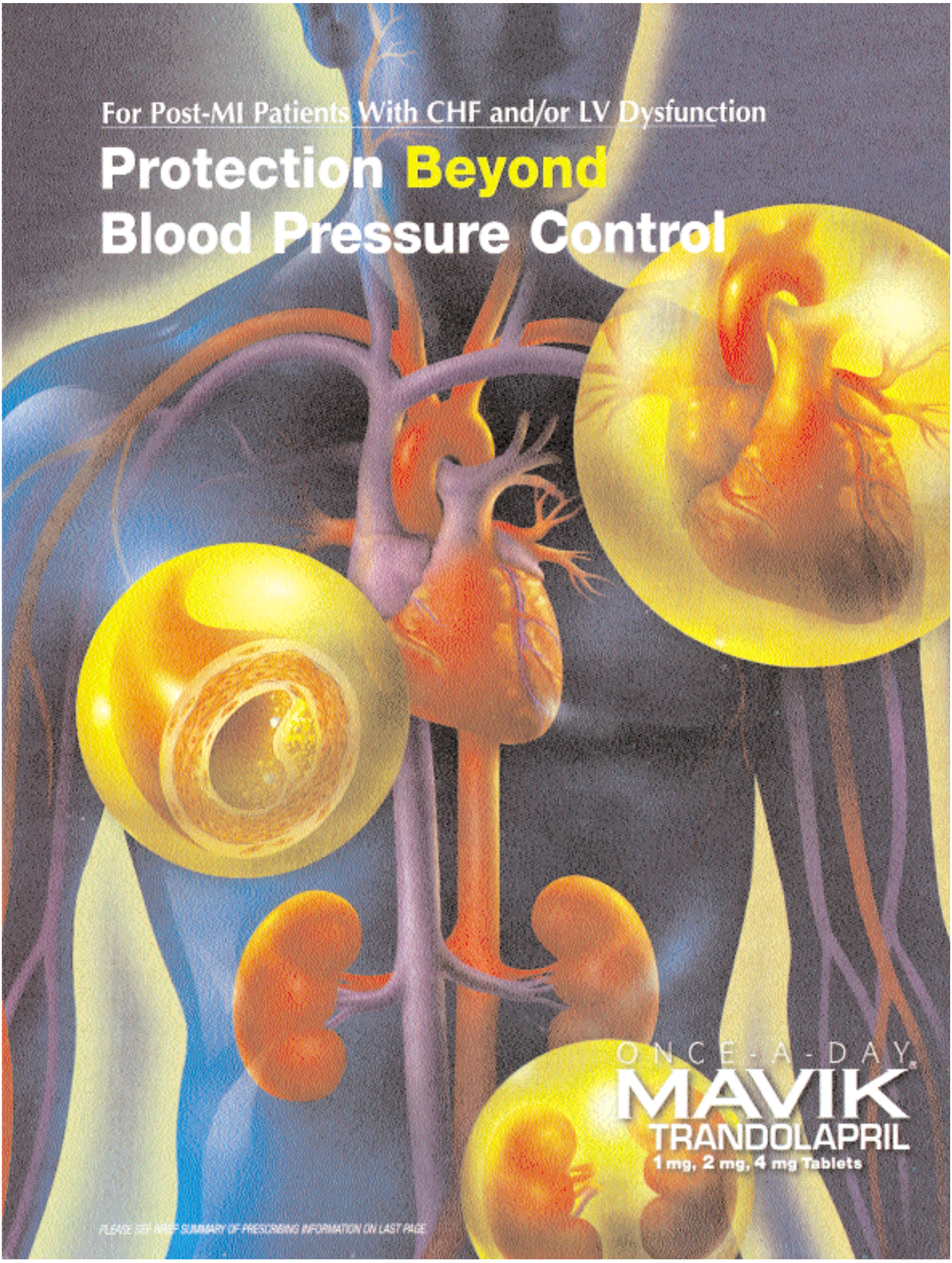
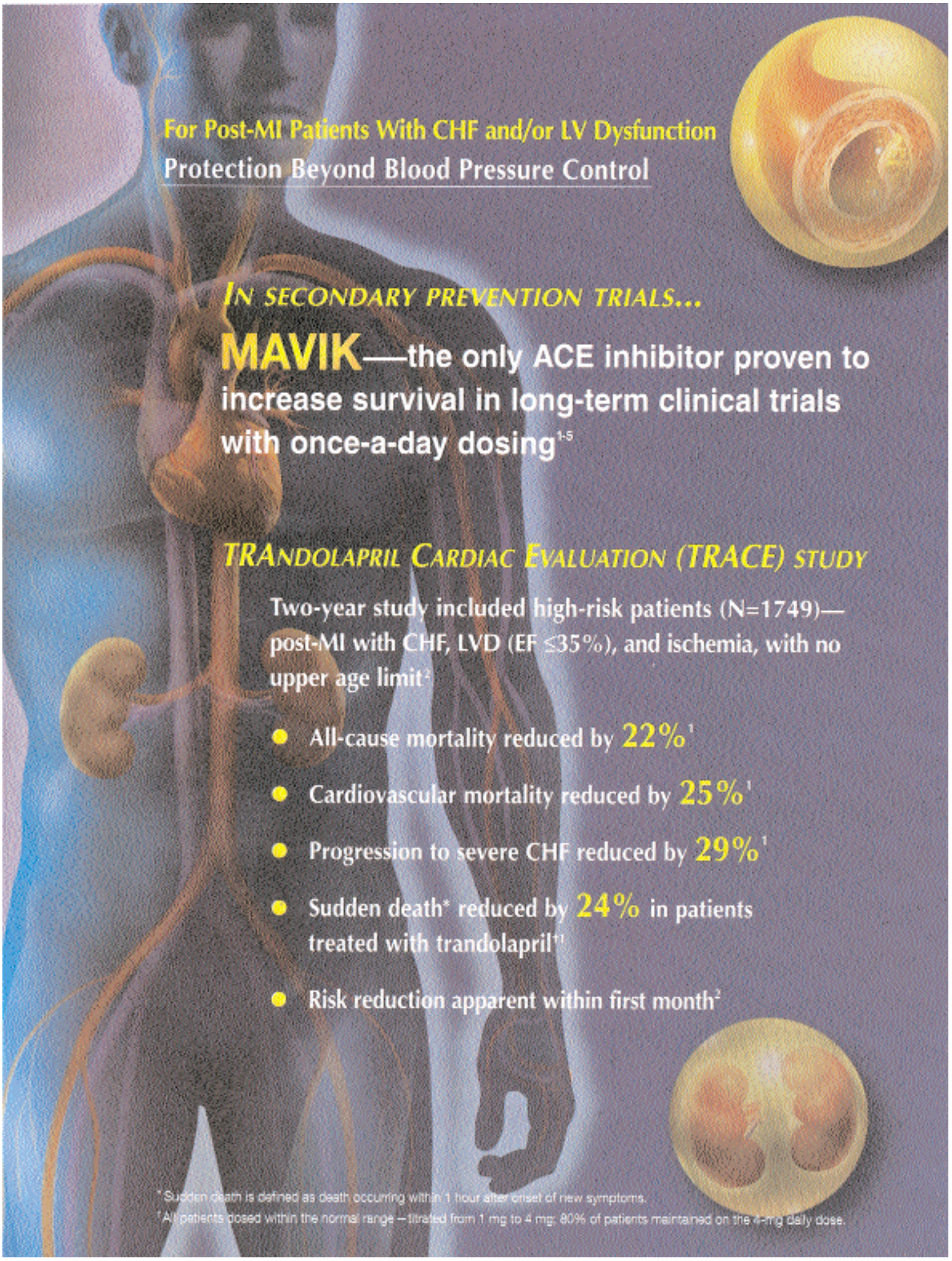
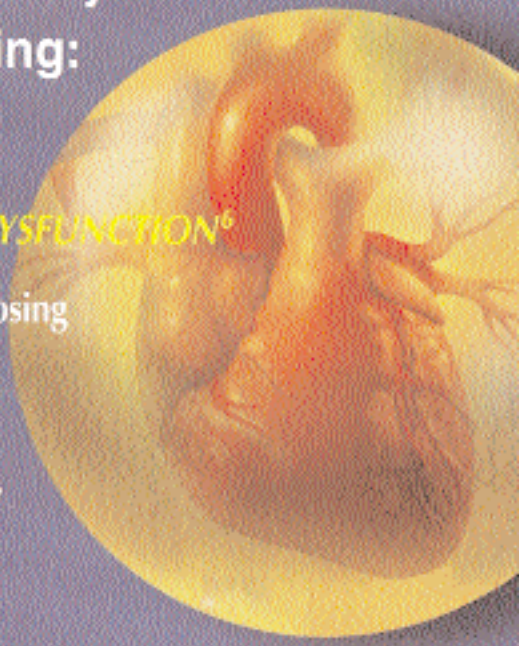

For Post-MI Patients With CHF and/or LV Dysfunction
Protection Beyond
Blood Pressure Control
ONCE-A-DAY
MAVIK
TRANDOLAPRIL
1 mg, 2 mg, 4 mg Tablets
PLEASE SEE BRIEF SUMMARY OF PRESCRIBING INFORMATION ON LAST PAGE


For Post-MI Patients With CHF and/or LV Dysfunction
Protection Beyond Blood Pressure Control
IN SECONDARY PREVENTION TRIALS...
MAVIK—the only ACE inhibitor proven to increase survival in long-term clinical trials with once-a-day dosing[1-5]
TRANDOLAPRIL CARDIAC EVALUATION (TRACE) STUDY
Two-year study included high-risk patients (N=1749)—post-MI with CHF, LVD (EF ≤35%), and ischemia, with no upper age limit[4]
All-cause mortality reduced by 22%[1]
Cardiovascular mortality reduced by 25%[1]
Progression to severe CHF reduced by 29%[1]
Sudden death* reduced by 24% in patients treated with trandolapril[1†]
Risk reduction apparent within first month[2]
* Sudden death is defined as death occurring within 1 hour after onset of new symptoms.
† All patients dosed within the normal range—titrated from 1 mg to 4 mg; 80% of patients maintained on the 4-mg daily dose.

MAVIK—proven efficacy and safety in a broad range of patients including:



POST-MI PATIENTS WITH CHF AND/OR LV DYSFUNCTION[6]

- Proven to increase survival with once-a-day dosing

NEWLY DIAGNOSED HYPERTENSIVE PATIENTS

- Flexible once-a-day dosing options with 1-mg, 2-mg, and 4-mg dosage strengths

DIABETIC HYPERTENSIVE PATIENTS

- Proven to significantly reduce proteinuria in type 2 diabetics with once-a-day dosing[7]

BLACK HYPERTENSIVES AND LOW-RENIN PATIENTS[8,9]

- Proven effective in black hypertensive patients[9]
- Proven equally safe and effective in young and old patients[10]

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, MAVIK should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality in the package insert.

The most commonly reported side effects were cough (1.9%), dizziness (1.3%), and diarrhea (1.0%). The incidence of side effects in the high-risk patient population in the TRACE post-MI study was higher than that in the hypertension studies. Headache and fatigue occurred in >1% but were reported more often on placebo. MAVIK is contraindicated in patients who are hypersensitive to this product or to any other ACE inhibitor. Angioedema has been reported in patients treated with ACE inhibitors.

References: 1. Kober L, Torp-Pedersen C, Carlsen JE, et al, for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 1995;333:1670-1676. **2.** Torp-Pedersen C, Kober L, Carlsen J, on behalf of the TRACE Study Group. Angiotensin-converting enzyme inhibition after myocardial infarction: The trandolapril Cardiac Evaluation Study. *Am Heart J.* 1996;132:235-243. **3.** Hall AS, Murphy GD, Ball SG, on behalf of the AIRE Study Investigators. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. *Lancet.* 1997;349:1493-1497. **4.** The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 1992;327:685-691. **5.** Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 1992;327:669-677. **6.** Torp-Pedersen C, Kober L, for the TRACE Study Group. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left ventricular function after acute myocardial infarction. *Lancet.* 1999;354:9-12. **7.** Bakris GL, Weir M, DeQuattro V, Rosendorff C, McMahon G, Retail. Hemodynamic and antiproteinuric responses to an ACE inhibitor trandolapril (T) or calcium antagonist, verapamil (V), alone or in fixed dose combination in patients with diabetic nephropathy: a randomized multicenter study [abstract]. *J Am Soc Nephrol.* 1998;7:1548. Abstract A1470. **8.** Data on file, Knoll Pharmaceutical Company. **9.** Weir MR, Gray JM, Fisher R, Saunders E, for the Trandolapril Multicenter Study Group. Differing mechanisms of action of angiotensin-converting enzyme inhibition in black and white hypertensive patients. *Hypertension.* 1995;26:124-130. **10.** Amar P, Wade A, Englert P, et al. Pharmacokinetics and pharmacodynamics of trandolapril after repeated administration of 2 mg to young and elderly patients with mild-to-moderate hypertension. *J Cardiovasc Pharmacol.* 1994;23(suppl 4):S44-S49.

ONCE-A-DAY
MAVIK®
TRANDOLAPRIL

Protection Beyond Blood Pressure Control

PLEASE SEE BRIEF SUMMARY OF PRESCRIBING INFORMATION ON LAST PAGE.

MAVIK®

(trandolapril) tablets

Brief Summary: Consult package insert for full prescribing information.

CONTRAINDICATIONS

MAVIK® is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions: Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors, including MAVIK®, may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors including MAVIK®. Symptoms suggestive of angioedema or facial edema occurred in 0.13% of MAVIK®-treated patients. Two of the four cases were life-threatening and resolved without treatment or with medication (corticosteroids). Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with MAVIK® should be discontinued immediately, the patient treated in accordance with accepted medical care and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, emergency therapy, including but not limited to subcutaneous epinephrine solution 1:1,000 (0.3 to 0.5 mL) should be promptly administered.** (See **PRECAUTIONS**, Information for Patients and **ADVERSE REACTIONS**.)

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension: MAVIK® can cause symptomatic hypotension. Like other ACE inhibitors, MAVIK® has only rarely been associated with symptomatic hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been salt- or volume-depleted as a result of prolonged treatment with diuretics, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating treatment with MAVIK®. (See **PRECAUTIONS**, Drug Interactions, and **ADVERSE REACTIONS**.) In controlled and uncontrolled studies, hypotension was reported as an adverse event in 0.6 percent of patients and led to discontinuations in 0.1% of patients.

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia, and rarely, with acute renal failure and death. In such patients, MAVIK® therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely during the first 2 weeks of treatment and, thereafter, whenever the dosage of MAVIK® or diuretic is increased. (See **DOSAGE** and **ADMINISTRATION**.) Care in avoiding hypotension should also be taken in patients with ischemic heart disease, aortic stenosis, or cerebrovascular disease.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of MAVIK® or required concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of trandolapril are insufficient to show that trandolapril does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen-vascular disease and/or renal disease should be considered.

Hepatic Failure: ACE inhibitors rarely have been associated with a syndrome of cholestatic jaundice, fulminant hepatic necrosis, and death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of trandolapril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, trandolapril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy.

Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal functions.

Doses of 0.8 mg/kg/day (9.4 mg/m²/day) in rabbits, 1000 mg/kg/day (11000 mg/m²/day) in rats, and 25 mg/kg/day (295 mg/m²/day) in cynomolgus monkeys did not produce teratogenic effects. These doses represent 13 and 5 times (rabbits), 1250 and 2564 times (rats), and 312 and 168 times (monkeys) the maximum projected human dose of 4 mg based on body-weight and body-surface-area, respectively, assuming a 50 kg woman.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including MAVIK®, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACE inhibitors have been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or the ACE inhibitor may be required.

Evaluation of hypertensive patients should always include assessment of renal function. (See **DOSAGE** and **ADMINISTRATION**.)

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium > 6.00 mEq/L) occurred in approximately 0.4 percent of hypertensive patients receiving MAVIK®. In most cases, elevated serum potassium levels were isolated values, which resolved despite continued therapy. None of these patients were discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with MAVIK®. (See **PRECAUTIONS**, Drug Interactions.)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials of trandolapril, cough was present in 2% of trandolapril patients and 0% of patients given placebo. There was no evidence of a relationship to dose.

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, MAVIK® will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with ACE inhibitors, including MAVIK®. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Symptomatic Hypotension: Patients should be cautioned that light-headedness can occur, especially during the first days of MAVIK® therapy, and should be reported to a physician. If actual syncope occurs, patients should be told to stop taking the drug until they have consulted with their physician. (See **WARNINGS**.)

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting, resulting in reduced fluid volume, may precipitate an excessive fall in blood pressure with the same consequences of light-headedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor that has a long duration of action.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician. (See **PRECAUTIONS**.)

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with MAVIK® is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may experience an excessive reduction of blood pressure after initiation of therapy with MAVIK®. The possibility of exacerbation of hypotensive effects with MAVIK® may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with MAVIK®. If it is not possible to discontinue the diuretic, the starting dose of trandolapril should be reduced. (See **DOSAGE** and **ADMINISTRATION**.)

Agents increasing serum potassium: Trandolapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes concomitantly with ACE inhibitors can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be used with caution and with appropriate monitoring of serum potassium. (See **PRECAUTIONS**.)

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: No clinically significant interaction has been found between trandolapril and food, cimetidine, digoxin, or furosemide. The anticoagulant effect of warfarin was not significantly changed by trandolapril.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted with oral trandolapril administered by gavage to mice (78 weeks) and rats (104 and 106 weeks). No evidence of carcinogenic potential was seen in mice dosed up to 25 mg/kg/day (85 mg/m²/day) or rats dosed up to 8 mg/kg/day (60 mg/m²/day). These doses are 313 and 32 times (mice), and 100 and 23 times (rats) the maximum recommended human daily dose (MRHDD) of 4 mg based on body-weight and body-surface-area, respectively assuming a 50 kg individual. The genotoxic potential of trandolapril was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosome aberration assays in Chinese hamster V79 cells, and the micronucleus test in mice. There was no evidence of mutagenic or clastogenic potential in these in vitro and in vivo assays.

Reproduction studies in rats did not show any impairment of fertility at doses up to 100 mg/kg/day (710 mg/m²/day) of trandolapril, or 1250 and 2500 times the MRHDD on the basis of body-weight and body-surface area, respectively.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and mortality.

Nursing Mothers

Radiolabeled trandolapril or its metabolites are secreted in rat milk. MAVIK® (trandolapril) should not be administered to nursing mothers.

Geriatric Use

In placebo-controlled studies of MAVIK®, 31.3% of patients were 60 years and older, 26.1% were 65 years and older, and 2.3% were 75 years and older. No overall differences in effectiveness or safety were observed between these patients and younger patients. (Greater sensitivity of some older individual patients cannot be ruled out).

Pediatric Use

The safety and effectiveness of MAVIK® in pediatric patients have not been established.

ADVERSE REACTIONS

The safety experience in U.S. placebo-controlled trials included 1867 hypertensive patients, of whom 831 received MAVIK®. Nearly 200 hypertensive patients received MAVIK® for over one year in open-label trials. In controlled trials, withdrawals for adverse events were 2.1% on placebo and 1.4% on MAVIK®. Adverse events considered at least possibly related to treatment occurring in 1% of MAVIK®-treated patients and more common on MAVIK® than placebo, pooled for all doses, are shown below, together with the frequency of discontinuation of treatment because of these events.

ADVERSE EVENTS IN PLACEBO-CONTROLLED TRIALS occurring at 1% or greater

	MAVIK (N=832) % Incidence (% Discontinuance)	PLACEBO (N=237) % Incidence (% Discontinuance)
Cough	1.9 (0.1)	0.4 (0.4)
Dizziness	1.3 (0.2)	0.4 (0.4)
Diarrhea	1.0 (0.0)	0.4 (0.0)

Headache and fatigue were all seen in more than 1% of MAVIK®-treated patients but were more frequently seen on placebo. Adverse events were not usually persistent or difficult to manage.

Left Ventricular Dysfunction Post Myocardial Infarction: Adverse reactions related to Mavik®, occurring at a rate greater than that observed in placebo-treated patients with left ventricular dysfunction, are shown below. The incidences represent the experience from the Placebo Controlled Mortality Study (TRACE). The follow-up time was between 24 and 56 months (the study duration).

Percentage of Patients with Adverse Events Greater Than Placebo; Trandolapril (n=878) vs Placebo (n=873): Cough, 26 vs 22; **Dizziness,** 20 vs 17; **Hypotension,** 11 vs 6.8; **Elevated serum uric acid,** 12 vs 10; **Elevated BUN,** 3.0 vs 1.6; PCA or CABG, 7.3 vs 6.1; **Dyspepsia,** 6.4 vs 6.0; **Syncope,** 5.0 vs 3.3; **Hyperkalemia,** 5.2 vs 2.8; **Bradycardia,** 4.7 vs 4.4; **Hypocalcemia,** 4.7 vs 3.0; **Myalgia,** 4.7 vs 3.5; **Elevated Creatinine,** 4.7 vs 2.6; **Gastritis,** 4.2 vs 3.6; **Cardiogenic shock,** 3.8 vs 2; **Intermittent claudication,** 3.6 vs 2; **Stroke,** 3.2 vs 3.2; **Asthenia,** 3.3 vs 2.6

Clinical adverse experiences (possibly or probably related or of uncertain relationship to therapy) occurring in 0.3% to 1.0% (except as noted) of the patients treated with MAVIK® (with or without concomitant calcium ion antagonist or diuretic) in controlled or uncontrolled trials (N=1134) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the total events are in bold) include (listed by body system):

General Body Functions: chest pain.

Cardiovascular: AV first degree block, bradycardia, edema, flushing, hypotension, palpitations.

Central Nervous System: drowsiness, insomnia, paresthesia, vertigo.

Dermatologic: pruritus, rash, pemphigus.

Eye, Ear, Nose, Throat: epistaxis, throat inflammation, upper respiratory tract infection.

Emotional, Mental, Sexual States: anxiety, impotence, decreased libido.

Gastrointestinal: abdominal distention, abdominal pain/cramps, constipation, dyspepsia, diarrhea, vomiting, pancreatitis.

Hemopoietic: decreased leukocytes, decreased neutrophils.

Metabolism and Endocrine: increased creatinine, decreased potassium, increased SGPT (ALT).

Musculoskeletal System: extremity pain, muscle cramps, gout.

Pulmonary: dyspnea.

Angioedema: Angioedema has been reported in 4 (0.13%) patients receiving MAVIK® in U.S. and foreign studies. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with MAVIK® should be discontinued and appropriate therapy instituted immediately. (See **WARNINGS**.)

Hypotension: In hypertensive patients, symptomatic hypotension occurred in 0.6 percent and near syncope occurred in 0.2 percent. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients.

Fetal/Neonatal Morbidity and Mortality: See **WARNINGS**, Fetal/Neonatal Morbidity and Mortality.

Cough: See **PRECAUTIONS**, Cough.

Clinical Laboratory Test Findings

Hematology: (See **WARNINGS**.) Low white blood cells, low neutrophils, low lymphocytes, thrombocytopenia.

Serum Electrolytes: Hyperkalemia (See **PRECAUTIONS**.) hyponatremia.

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.1 percent of patients receiving MAVIK® alone and 7.3 percent of patients treated with MAVIK®, a calcium ion antagonist and a diuretic. Increases in blood urea nitrogen levels occurred in 0.6 percent of patients receiving MAVIK® alone and 1.4 percent of patients receiving MAVIK®, a calcium ion antagonist, and a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those prefavored with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See **PRECAUTIONS** and **WARNINGS**.)

Liver function tests: Occasional elevation of transaminases at the rate of 3X upper normals occurred in 0.8% of patients and persistent increase in bilirubin occurred in 0.2% of patients. Discontinuations for elevated liver enzymes occurred in 0.2 percent of patients.

MAV00-3052/7-00 BC0727B Printed in USA

Knoll Pharmaceutical Company
3000 Continental Drive - North
Mount Olive, NJ 07828-1234

Kos Pharmaceuticals, Inc.

BASF Pharma

knoll

Sherwood L. Gorbach, M.D.

The development of probiotics in the past decade has signaled an important advance in the food industry - the marriage of consumer foods with mainstream science. The term probiotic, popularized by R. Fuller in 1992, was defined recently by an Expert Committee as "Living microorganisms which upon ingestion in certain numbers exert health benefits beyond inherent general nutrition."

Medical Research and Practice Updates

THE DEVELOPMENT OF LACTOBACILLUS GG, THE FIRST PROBIOTIC OF THE NEW ERA

This definition sets the requirements that the microorganisms must be alive, not pasteurized, and present in high numbers, generally more than one billion per daily ingested dose. Health benefits must be established by scientific testing in humans performed by legitimate research groups and then published in peer-reviewed biomedical journals. The probiotic microorganisms consist mostly of Lactobacillus, Bifidobacterium and Streptococcus, types that have been used since recorded history in the production of fermented dairy products.

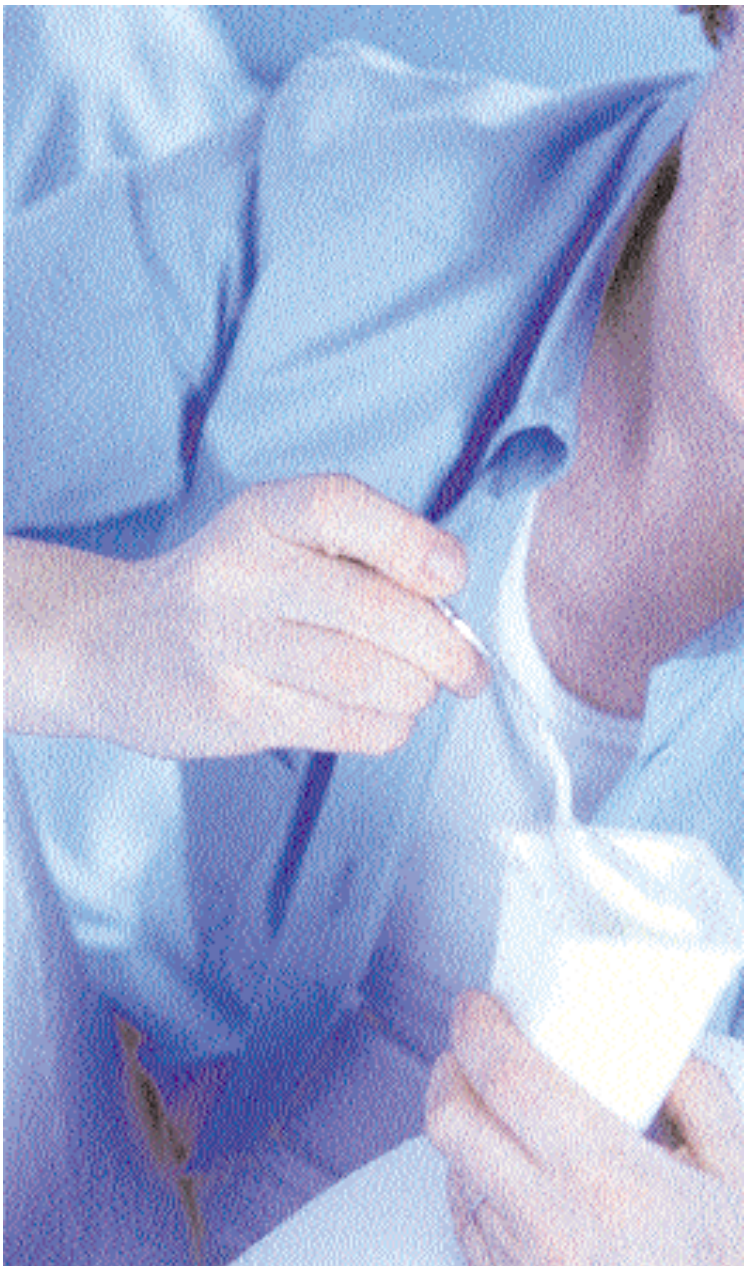
I began my laboratory research in this field in 1964 with what turned out to be a futile effort to implant a dairy strain of Lactobacillus acidophilus in the intestine of humans. Over the next two decades I tried similar studies with newly developed dairy strains of Lactobacillus, and this work proved unsuccessful as well. It became clear by 1983 that the Lactobacillus strains used traditionally in the dairy industry, e.g., L. bulgaricus, L. casei, and L. acidophilus, did not possess biological characteristics that would enable them to consistently implant in the intestine of humans. Our research over the previous 20 years had established that implantation in the bowel was the critical feature that a strain must possess in order to influence the intestinal milieu. Since none of these strains had the ability to implant the human gut, they could not be expected to have any effect on human health. Therefore, we wrote down a list of the desirable properties of an ideal Lactobacillus strain that would benefit human health and could be used in the dairy industry (Table 1). Working now with my colleague, Dr. Barry Goldin, we spent the next two years in the search for a naturally occurring Lactobacillus strain in the microflora of a healthy human being that satisfied these requirements. Members of our laboratory staff and our friends contributed stool specimens so that we could search for our ideal strain.

The first requirement we set for a candidate Lactobacillus strain was stability in acid and bile, a property that was needed in order to traverse the portal of entry (mouth, stomach and upper intestine) where gastric acidity and gall bladder bile would destroy ingested bacteria. While most lactobacilli are relatively resistant to acid and bile, we required a higher degree of stability to these noxious substances in our ideal strain. The strains that survived the acid/bile requirement were submitted to the next, and most important test, adherence to human intestinal cells. Isolated human intestinal cells were placed in an adherence column, and candidate Lactobacillus strains were passed over the cells. After washing, the

attached lactobacilli were cultured from the intestinal cells. We now had a collection of lactobacilli that were resistant to acid and bile and had demonstrated adherence to human intestinal epithelial cells.

With this collection of candidate lactobacilli, we tested for production of an antimicrobial substance that was active against various bacteria from the normal intestinal microflora as well as pathogenic bacteria. The lactobacilli that produced the greatest antimicrobial activity against such bacteria as E. coli, Streptococcus, Clostridium and Salmonella were then assayed for the final criterion – good growth rate – a necessary property for commercial development. Many lactobacilli have slow growth or possess fastidious growth requirements, factors that would cause difficulty in industrial-scale production.

In the spring of 1985 we isolated a strain that satisfied all of these stated conditions. As a bonus, the selected strain had a unique colonial morphology that made it easy to identify in a mixed culture of other lactobacilli and streptococci such as encountered in fecal cultures. This property has allowed investigators to make quantitative and qualitative counts of the strain in a mixed-culture setting. According to the most recent taxonomy, the strain is now classified as L. rhamnosus. It can be identified in the laboratory by standard sugar fermentations, molecular analysis and PCR tests. The strain was given the common name, Lactobacillus GG (LGG), for the discoverers, Gorbach and Goldin. LGG was deposited in the American Type Culture Collection, with the accession number 53103. A patent application was submitted that year, and it was issued in 1987 in the USA and subsequently in many other countries. It is fair to say that LGG was the first of the new generation of probiotic strains, and it was in fact discovered before the term was popularized. The criteria listed in Table 1 are now recognized as the basis for development of new probiotic strains, which have later been introduced by several dairy companies.



Health Effects

The discovery of the LGG strain, which satisfied all of our criteria for an ideal strain, was only the first step in the process of developing a new microorganism for use in the food industry. We had pledged from our first moments on this project that any claims about this strain, whether microbiological or clinical, would require verification by scientific data that were subjected to the scrutiny of fellow researchers at international meetings and then published in professional journals. The past history of research on fermented dairy products has been a sorry tale of extravagant claims and unsubstantiated declarations of efficacy. It was our goal that LGG would undergo rigorous scientific study by independent investigators.

The first publication in 1987, which presented the data on the antimicrobial substance and the general properties of the strain, was published in *Antimicrobial Agents and Chemotherapy*, a primer journal of the American Society for Microbiology. The next topic for study was implantation in the GI tract of humans. Studies in the USA and Finland established the colonization of LGG in healthy as well as sick persons. Following these basic studies, several investigators undertook the investigations of efficacy in a variety of human illnesses. The Finnish

dairy, Valio Ltd., was granted an exclusive license for LGG in 1987, and they spearheaded the extensive research effort. Drs. Kari Salminen and Maija Saxelin, followed later by Drs. Annika Mäyrä-Mäkinen and Riitta Korpela, were the major architects of the research effort at Valio. The initial scientific studies were conducted by Finnish university scientists, Drs. Erika Isolauri and Seppo Salminen. Over the past 13 years, over 100 research papers have been published on LGG in scientific journals, along with scores of books, monographs, and doctoral theses. The scientists work in universities and research institutes throughout the world, including 10 European countries, such as Finland, United Kingdom and Italy, and the USA, Peru, Thailand, Pakistan, Estonia, Russia and Japan. (A complete listing of published articles can be found at http://www.valio.fi/lgg/index.shtml.) Currently, over 30 investigations of LGG are ongoing in several countries, dealing with a variety of human conditions for which this probiotic might offer some benefit.

Proven benefits of LGG (Table 2)

The first studies established efficacy of LGG in reducing the severity and shortening the duration of symptoms of acute diarrhea in children, mostly caused by rotavirus infection, the commonest form of this illness. These positive results were confirmed by more than 10 subsequent studies, including a large multicenter trial in 13 pediatric centers in 10 European countries, conducted by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); in this study, LGG was administered with the standard oral rehydration solution. Other studies showed that diarrhea could be prevented in children attending day care facilities. Two recent studies, conducted in the USA and Finland, showed that intestinal side effects and diarrhea could be reduced by two-thirds in children receiving antibiotics for various infections. Travelers' diarrhea was cut nearly in half by preventative consumption of LGG in a group of tourists from New York who were traveling to high-risk locations.

Substantial evidence but needing additional proof

LGG has been used with positive effects in young children with food allergies, generally to cows' milk and other animal protein. These problems arise in children who are weaned early from the breast to cows' milk or in others who develop chronic intestinal problems after a bout of rotavirus diarrhea. Besides the abdominal pain and discomfort experienced by these children, many also develop the uncomfortable skin condition known as Eczema. Placebo-controlled studies from Finland have shown excellent results with LGG. A recent publication in *The Lancet* from the Finnish investigators led by Dr. Erika Isolauri showed that feeding LGG to pregnant women in their final month of pregnancy and then to the infants for six months prevented the development of eczema by 50% (from 46% incidence in the placebo group to 23% in the LGG group) when examined over the period of two years. In other studies travelers' diarrhea was cut nearly in half in one study by preventative consumption of LGG in a group of tourists from New York who were traveling to high-risk locations; additional studies

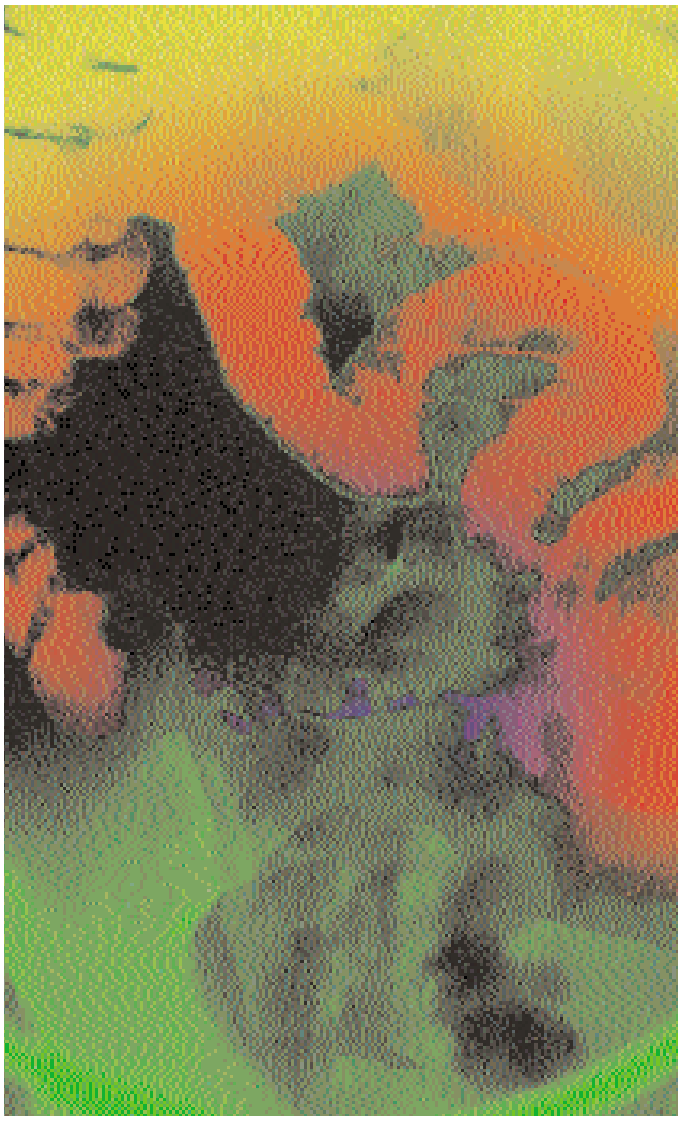
which incorporate microbiology findings need to be done on this topic. Two studies, one from Finland and the other from Brazil, have been presented at scientific meetings, which have shown significant prevention of respiratory infections in children attending day care centers. The protective effects resulted in lower rates of absenteeism and fewer courses of antibiotics in the children receiving LGG in milk compared to a placebo group. A recent study in children receiving LGG milk showed reduction in the rate of caries and lower counts of Streptococcus mutans, the oral bacteria held responsible for tooth decay in children. Based on preliminary studies that showed promise, several researchers are using LGG to treat and prevent vaginitis, a common and difficult problem affecting many women of child-bearing age.

Ongoing research

Four studies in the USA, Finland and Italy are under way to study LGG in Crohn's disease, a particularly severe form of inflammatory bowel disease. These are multicenter studies, using a placebo-controlled design, conducted by leading university researchers. Ulcerative colitis is also being investigated in other centers. A preliminary study from Italy showed good results with LGG in cystic fibrosis in terms of lessening the intestinal problems, reducing acute respiratory incidents and producing weight gain. This work is being repeated with a larger group in Italy, and the same protocol is also under study in the USA. Based on encouraging, but uncontrolled studies, the development of antibiotic-associated diarrhea in adults produced by Clostridium difficile, the major cause of hospital-associated diarrhea in the USA and Europe, is under investigation by at least four groups, using a LGG vs. placebo design.

Future areas of research

With regard to probiotics, it can be said that the future is better than it used to be. LGG has shown good results in an animal model of chemically induced colon cancer, based on the modulation by LGG of cancer-inducing enzymes in the intestinal microflora. Since this animal model is felt to mimic the human disease rather closely, this work should be followed up with human trials. New studies have shown that the intestinal flora can influence the progress of rheumatoid arthritis, and this opened the possibility of altering the microflora favorably by LGG, thereby modulating the clinical expression of this disease. Preliminary studies are planned. Ulcer disease caused by Helicobacter pylori, irritable bowel syndrome and constipation are being studied by several investigators, but results are not yet available.



The consumer's perspective

High science notwithstanding, the consumer needs to receive a message about the probiotic that is comprehensible and reasonable, without appearing to be exaggerated. In addition, these "health claims" must be defensible when placed under scrutiny by the controlling authorities. The recitation of LGG efficacy in various disease states would imply to the consumer that the benefit is only in terms of curing a medical condition that is not necessarily present. In addition, such claims would be rejected by the health authorities because they would position the product as a "drug." Most important, this medical approach fails to emphasize the major advantages of probi-

otics to the usual consumer, which are in the realm of maintenance of health and prevention of disease. Table 3 lists the items cited on the packages of LGG products in Finland and the USA, and have been accepted by the local authorities. Similar statements appear in promotional materials in many of the other countries in which LGG is sold. While the statements are made in non-technical terms, each claim is supported by an abundant array of published articles. These scientific studies are important to provide credibility with physicians, health authorities and informed consumers. Without the backing of such research, the probiotic should not be allowed to make any claims in the health arena. Finally, the consumer requires good taste and high quality; absent these critical features, no amount of science could sell a probiotic food product.

Conclusion

The discovery of LGG was based on a calculated strategy of considering the characteristics of an ideal probiotic strain, and then asking Nature to provide it within the diversity of the microbial world. We must persevere in our pursuit of discovering new applications of LGG that will bring benefits to humankind. The research work on LGG continues.

Table 1

CRITERIA FOR AN IDEAL LACTOBACILLUS STRAIN FOR USE IN THE DAIRY INDUSTRY*

- Resist to acid and bile
- Attachment to human epithelial cells
- Colonize the human intestine
- Produce an antimicrobial substance
- Good growth characteristics
- Beneficial effects of human health

List created in 1983 that led to discovery of Lactobacillus GG

Table 2

HEALTH BENEFITS OF LGG

Proven Benefits

- Treat and prevent acute diarrhea and gastroenteritis
- Prevent antibiotic-associated intestinal side effects and diarrhea

Substantial Evidence, But Needs Additional Proof

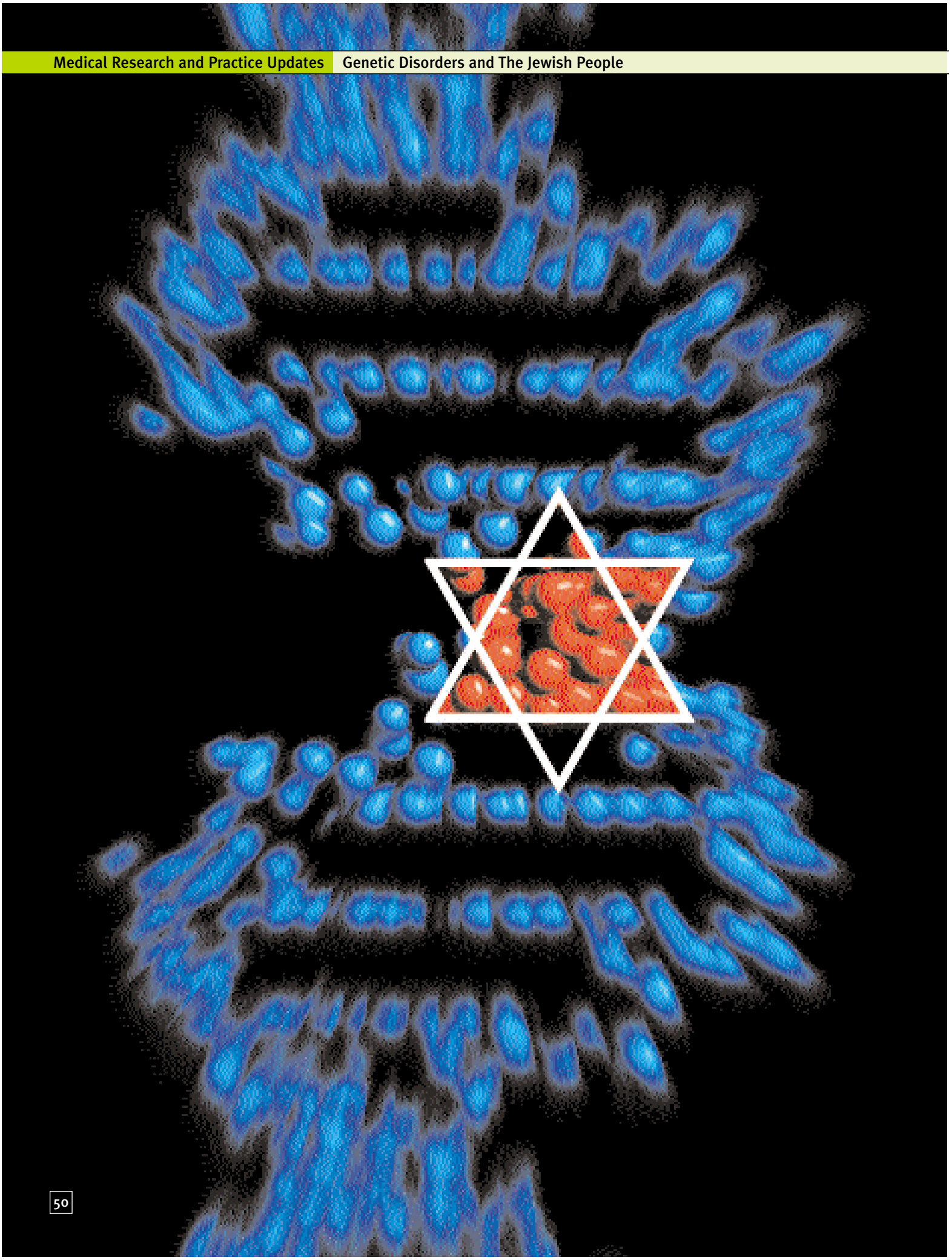
- Treat and prevent food allergy and related eczema
- Prevent respiratory infections among children in day care centers
- Prevent caries in children
- Treat and prevent vaginitis
- Prevent travelers' diarrhea

Ongoing Research In Promising Areas

- Treat and prevent relapses in Crohn's disease and ulcerative colitis
- Reduce intestinal symptoms and respiratory episodes in children with cystic fibrosis
- Treat and prevent antibiotic-associated diarrhea caused by Clostridium difficile in hospitalized patients

Future Areas Of Research

- Prevent colon cancer (only animal data available)
- Treat rheumatoid arthritis
- Treat ulcers caused by Helicobacter pylori
- Treat irritable bowel syndrome
- Relieve constipation



Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H.
Director, Center for Human Genetics,
Professor of Human Genetics, Pediatrics, Pathology and Obstetrics & Gynecology
Boston University School of Medicine

About 1 in 20 people in this geographic isolate are totally color blind (total achromatopsia) and about half of the population are carriers of the gene for this autosomal recessive disorder. Visual impairment, nystagmus and photophobia, are the primary concomitants of this otherwise rare disorder.

Medical Research and Practice Updates

GENETIC DISORDERS AND THE JEWISH PEOPLE

These remarkable incidence figures apply to the highly inbred population of the island of Pingelap in the Pacific. This otherwise rare disorder was introduced into this island population by a sailor. Thereafter, following a typhoon that almost wiped out the population, inbreeding spread the gene through the few inhabitants that were left, to eventually become part of the entire island's gene pool through the ensuing years.

This example of achromatopsia on a Pacific atoll illustrates two critical points. The first is known as the founder effect, in which a visiting sailor introduced a new gene mutation into a population group where this specific disorder had never been seen. The second point is the inbreeding effect, resulting in the spread of recessive gene through a close-knit population.

While a founder effect may be important so far as the introduction of new gene is concerned, a de novo gene mutation is also a not infrequent event. Either way, the spread of gene mutations is facilitated by breeding within close-knit populations. Hence,there are many examples of specific genetic disorders segregating within recognizable ethnic groups (Table 1). Clearly, then, there is no ethnic or racial group without their own "genetic burden." Segregation of harmful gene mutation within that group may not necessarily be unique, given the frequency of unions between all ethnic and racial groups. The occurrence of an autosomal recessive disorder simply means that the harmful gene mutation was inherited from each parent equally and that for each pregnancy by such a couple, there is a 25% risk of having an affected offspring.

It should be obvious, then, that the occurrence of certain recessive disorders among the Jewish people is not unique (all described disorders have occurred in non-Jews), but simply reflects childbearing among couples of Jewish ancestry. Recent concerns expressed by rabbinical and other Jewish leaders about the number of described genetic disorders among the Jewish people prompting possible stigmatization, should be laid to rest. The appropriate perspective is the realization that over 8,500 monogenic disorders and traits have been catalogued,only a tiny handful of which have been described with significant frequency among the Jewish people. This focus of discovery also reflects the intense desire among Jewish couples to seek out as much information as possible in planned childbearing resulting in the stimulation of research and volun-

teerism that culminated in the advanced knowledge of genetic disease thus far achieved in this ethnic group. The reality is that important life-threatening genetic disorders may occur with similar or greater frequency in other ethnic or racial groups. For example, about 1 in 10 whites carry one of the three gene mutations for autosomal recessive hemochromatosis, with close to 1 in 200 born affected. About 1 in 25 whites carry gene mutation for cystic fibrosis, about 1 in 2,500 being born affected by this potentially lethal disorder. These insights should help dispel any ideas of an unusual aggregation of harmful genes among the Jewish people.

Table 1. Selected single examples of genetic disorders found more commonly in specific ethnic groups.
(Excerpted from Your Genetic Destiny: Know Your Genes, Secure Your Health, Save Your Life, A. Milunsky, Perseus Books, Cambridge, 2001.)

Ethnic Group	Genetic Disorder
Africans	Sickle cell disease and other
	disorders of hemoglobin
Afrikaners	
(white South Africans)	Porphyria variegata
Amish/Mennonites	Ellis-Van Creveld syndrome
Armenians	Familial Mediterranean fever
Ashkenazi Jews	Tay-Sachs disease
Chinese	Thalassemia (alpha)
Eskimos	Congenital adrenal hyperplasia
Finns	Congenital nephrosis
French-Canadian	Neural-tube defects
Irish	Phenylketonuria
Italians	Fucosidosis
Japanese	Fukuyama congenital
	muscular dystrophy
Japanese and Korean	Acatalasia
Mediterraneans	Thalassemia (mainly beta)
(Italians, Greeks,	
Sephardic Jews,	
Armenians, Turks,	
Spaniards, Cypriots)	
Norwegians	Phenylketonuria

Genetics in clinical practice

It should already be self-evident that genetic disorders occur throughout all populations and that awareness by physicians of disorders that might be genetic has now become especially important, given the dramatic advances in human genetics over the past quarter of century. The Human Genome Project revealed that each of us has a set of 30,000-40,000 genes. While specific gene mutations for all known monogenic disorders are yet to be elucidated, routine DNA analysis now enables a vastly increasing array of tests, including diagnostic,carrier, predictive, prenatal and preimplantation analyses. Keeping abreast of all these new developments is important for the practicing clinician. Failure to keep up with this rapidly expanding area of knowledge will deprive individuals of precise diagnostic opportunities and invite litigation. Some important practical risk-management steps can be recommended (Table 2).

Draw a family tree to occupy the first page of an individual's medical record. Update the pedigree history at least annually or as often as circumstances dictate. Special notation should be made of recurrent miscarriages, any stillbirths, deaths in infancy, congenital malformations, mental retardation,cancers and chronic serious illness. On reading *Your Genetic Destiny: Know Your Genes, Secure Your Health, Save Your Life* (see insert),

Table 2. Risk-Management Steps for Genetic Disorders

1.	Construct a family pedigree.
2.	Note ethnic origins.
3.	Note consanguinity
4.	Develop a high degree of alertness, vis-à-vis genetic disorders.
5.	Request precise information to facilitate an accurate diagnosis.
6.	Establish contact with a Board-certified geneticist.
7.	Do not provide off-the-cuff genetic counseling and risk estimation.
8.	Refer for genetic evaluation and counseling.
9.	Offer/recommend appropriate genetic tests.
10.	Be sure to obtain results of tests ordered.
11.	Use a proven and reliable laboratory.
12.	Do not attempt interpretation or reinterpretation of genetic test results.
13.	Document all recommendations and steps taken.

the realization that "everything is genetic" will soon become apparent. Whether disorders are inherited or arise from environmental insults (nutritional, toxic, infectious, chemical, hypoxic, heat, etc.), all invoke the body's genetic mechanisms

that mollify, modify, attack, regulate or in some way influence occurrence, penetrance, expression, susceptibility, predisposition and severity of effects. Hence, disorders that are not inherited still involve each cell's genetic machinery. The physician must therefore be alert not only to known genetic disorders, but also to the more common multifactorial disorders, including congenital malformations, such as spina bifida.

Of vital importance is the ethnic origin of both sides of the family. This critical information is often not sought, thereby missing opportunities for carrier detection and the avoidance of pregnancies with offspring affected by serious/fatal genetic disorders. Notation of consanguinity is also important in assessing genetic risk.

In determining information to be incorporated in the family tree, requests for more precise information are important. Obtaining autopsy reports, discharge summaries, biopsy reports, X-ray or other imaging study reports, photographs, information about stored DNA or autopsy tissue, may all provide vitally important pieces of information for diagnosis and ultimate prevention of future catastrophes. No practicing clinician can be expected to master the full panoply of genetic disorders. However, every clinician can and should be held to a standard that requires contact with, or referral where appropriate to a clinical geneticist Board- certified by the American Board of Medical Genetics (and recognized by the American Medical Association as a formal specialty). This contact, for example, by telephone, will enable clinician to rapidly determine whether or not a particular condition in a family requires further study. Certainly, the clinician should otherwise refer for genetic evaluation and counseling where his/her knowledge may be incomplete. Personal insight into the limits of genetic knowledge may sometimes not be apparent, hence a safe course is either consultation by telephone or direct referral to a clinical geneticist.

Where a clinician plans to offer or recommend appropriate tests, care should be exercised in not interpreting or reinterpreting genetic test results. A Johns Hopkins University study showed that physicians would incorrectly interpret about one-third of DNA test results. All steps that may be taken relative to the detection/diagnosis of genetic disorder should be documented in the medical record. Needless to say, all of these recommendations for risk-management apply to consideration of genetic disorders, not only for those conditions among the Jewish people, but for all patients.

The reality is that important life-threatening genetic disorders may occur with similar or greater frequency in other ethnic or racial groups. For example, about 1 in 10 whites carry one of the three gene mutations for autosomal recessive hemochromatosis, with close to 1 in 200 born affected. About 1 in 25 whites carry a gene mutation for cystic fibrosis, about 1 in 2,500 being born affected by this potentially lethal disorder. These insights should help dispel any ideas of an unusual aggregation of harmful genes among the Jewish people.

Indicators of Genetic Disorders

In constructing a family pedigree, data review might reveal a particular pattern of inheritance,consanguinity or sexual predilection. In this way, autosomal dominant, autosomal recessive and sex-linked disorders might be revealed through the pattern of those affected. Classical imprinting effects might also be realized for dominant disorders, such as paraganglioma. In this condition, the children of both sexes of an affected mother might be affected, but none of the offspring of an affected male would have this disorder. The earlier the onset of any disorder, the more likely its genetic basis. In this context, the phenomenon of genetic anticipation is important, showing that for specific disorders, such as Huntington's disease, myotonic dystrophy and other conditions with dynamic mutations, may present earlier and earlier over each generation. Earlier onset and severity might also be related to the paternal or maternal origin of the specific gene mutation. Such would be the case for Huntington's disease of paternal origin, whereas infants born of mother affected by myotonic dystrophy would be seriously affected at birth. A history of recurrent miscarriage, stillbirth or deaths in infancy raises suspicions about chromosome disorders and biochemical/metabolic diseases. A history of mental retardation, especially in males on the maternal side, may raise questions about sex-linked mental retardation of which more than 60 defined syndromes are known. The observation of males with mental retardation on the mother's side and one or more females with premature menopause on the same side raises the possible diagnosis of the Fragile X syndrome. The occurrence of the same type of cancer in two related individuals obviously signals a possible genetic commonality. Less obvious, but equally important,are associations between different cancers caused by the same gene mutation. For example, gene mutations in the BRCA-1 and BRCA-2 breast cancer genes may cause not only breast and ovarian cancer,but also prostate,pancreatic and colon cancer. While advanced maternal age is associated with five particular

numerical chromosome disorders in the offspring of such mothers (trisomies 21,18,13 and triple X and Klinefelter syndrome), advanced paternal age may be associated with disorders such as Marfan syndrome, achondroplastic dwarfism, and myositis ossificans progressiva.

DNA analyses for carrier detection

The bible and the Talmud are replete with descriptions of obvious genetic disorders and congenital defects. Early on rabbis clearly recognized hemophilia A and proscribed circumcision of the fourth child if the first three sons died. By the twelfth century, Maimonides advised that if two sons who had been circumcised died, the third son should not be circumcised, at least not on the ritual eighth day of life. Maimonides must have already realized the sex-linked mode of inheritance, since he indicated that no circumcision should be done regardless of whether the son was from the first or second husband.

It is safe to say that no genetic disorders occur exclusively among the Jewish people. There are a number of monogenic disorders that occur with significant or high frequency, but may still be found among non-Jews. Particularly important molecular advances have facilitated carrier detection, especially during preconception care and subsequently for prenatal diagnosis. These new advances now present increasing opportunities to avoid both the conception or birth of children with lethal or seriously disabling genetic disorders. Discussion of a few of the routinely tested autosomal recessive genetic disorders serves to illustrate these opportunities for carrier detection.

1.Tay-Sachs disease. Between 1 in 27 and 1 in 30 Ashkenazi Jews are carriers of gene mutation causing this neurodegenerative disorder. DNA analysis of the five most common mutations detect about 99% of all carriers and is the preferred method over hexosaminidase A enzyme assay. French-Canadians, too, have a carrier rate of about 1 in 30. However, the common gene mutations harbored by French Canadians are mostly different from those found among Ashkenazi Jews. The ultra-orthodox Jewish community in New York established the Dor Yashorim program because of their highly restrictive laws about abortion. Since marriages are arranged in this community, individuals are screened early for Tay-Sachs disease and some other disorders before they are introduced to each other. A central agency controls the flow of anonymous test results retaining total privacy, thereby avoiding stigmatization, the marriage of two carriers (who would never be matched) and the virtual avoidance of the more common fatal genetic disorders in this group.

Ashkenazi Jewish population screening for Tay-Sachs disease between 1970 and 1999 covered 1.4 million individuals worldwide. About 51,000 individual carriers and 1,379 carrier couples have been identified. Prenatal diagnoses of 628 affected fetuses were made. As a result,the incidence of Tay-Sachs disease in the United States has dropped by over 90%.In fact, today more infants are born with this fatal disorder to non-Jewish couples or to mixed-marriage couples who have not been tested, than to Jewish couples. In the absence of testing, about 1 in 3,600 Ashkenazi Jewish births would be an affected infant.

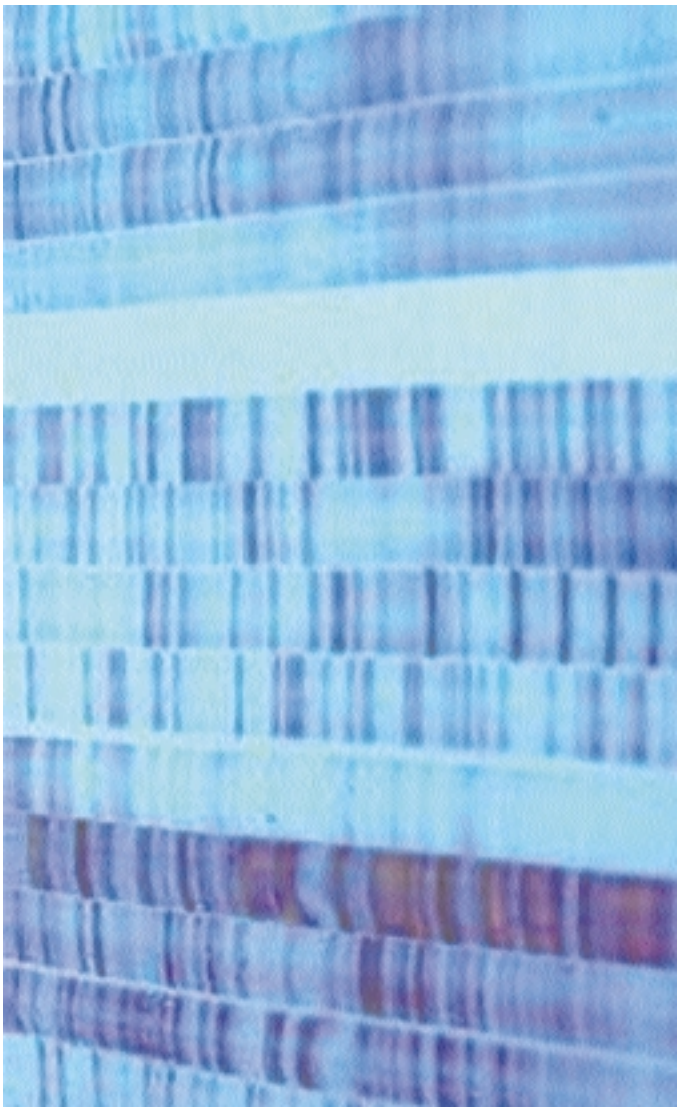
2.Gaucher's Disease. About 1 in 15 Ashkenazi Jews carry gene mutation for this autosomal recessive lysosomal enzyme storage disorder. Analysis for five mutations enables a detection rate of about 93%.

3.Canavans Disease (or spongioform encephalopathy). The carrier rate for this neurodegenerative disorder approximates 1 in 40 in the Ashkenazi population. Testing for the three most common gene mutations enables detection of bout 98%of all carriers.

4.Niemann-Pick Disease Type A. About 1 in 90 Ashkenazi Jews are carriers of gene mutation for this neurodegenerative disorder. Analysis of the three most common mutations provides a detection rate for carriers of over 95%.

5.Fanconi Anemia. Characteristic features include pancytopenia, hyperpigmentation, short stature and radial and renal defects. About 1 in 90 Ashkenazi Jews are carriers of this disorder. Not all features may be present in an affected individual and considerable variation in severity is common. There is a major predisposition to leukemia and lymphoma. Carrier detection for this autosomal recessive disorder and analysis of one mutation yields a detection rate of at least 95%.

6.Familial Dysautonomia. This protean disorder of the nervous system is characterized by marked autonomic dysfunction with signs present from birth and subsequent neurological deterioration. About 1 in 30 Ashkenazi Jews carry a gene mutation and DNA analysis of one mutation achieves over 99% detection rate.



7.Familial Mediterranean Fever. About 1 in 7 Sephardic Jews are carriers of this autosomal recessive disorder characterized by recurrent episodes of inflammation causing peritonitis, pleurisy and arthritis, frequently accompanied by fever, occasionally an erysipeloid eruption, and eventually by renal failure, if not treated. Analysis of the four most common mutations yields a carrier detection rate of about 85%. Since the advent of mutation analysis for Familial Mediterranean Fever, Ashkenazi Jews also have been found to be carriers, at a similar rate to that found among Sephardic Jews. However,for molecular reasons not entirely understood, clinical manifestations of this disorder are very infrequent among the Ashkenazi population. Early diagnosis is important, given the efficacy of treatment with colchicine, which, if given in a timely fashion, will prevent kidney failure due to amyloidosis.

8.Non-Syndromic Deafness. Sensorineural deafness due to mutation in the Connexin-26 gene ranks as the most common cause of hereditary deafness. About 1 in 26 Ashkenazi Jews carries a mutation in this gene, most frequently a specific deletion (167delT). Affected individuals have no other features or birth defects.

9.Bloom Syndrome. This disorder is characterized by immunodeficiency, photosensitivity,and increased risk for multiple cancers. About 1 in 104 Ashkenazim carry a gene mutation. Analysis of one mutation yields a detection rate of over 99%.

There are many more advances in molecular medicine beyond the needs and recommendations for carrier detection in the context of childbearing and the avoidance and prevention of genetic defects and mental retardation. Ranking high among these new advances are opportunities for predictive tests for breast/ovarian cancer (1 in 50 Ashkenazi women carry 1 of 3 mutations in the BRCA-1 and BRCA-2 genes) and for colon cancer (about 1 in 16 Ashkenazim carry a gene mutation in the familial polyposis coli gene). Given the enormous flow of information from the Human Genome Project that now has a direct impact on patient care, physicians are exhorted to make major efforts to become well informed about these remarkable advances.

Dr.Aubrey Milunsky is professor of human genetics,pediatrics, obstetrics and gynecology and pathology and director of the Center for Human Genetics at Boston University School of Medicine. He is a Fellow of the Royal College of Physicians of England. He is the author or co-author of more than 350 scientific communications. His major textbook, Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment (4th Edition), *of which he is the editor, is the worldwide reference text for prenatal diagnosis. Just published is his latest book for the lay press titled* Your Genetic Destiny: Know Your Genes, Secure Your Health, Save Your Life, Perseus Publishing Group, Cambridge, MA.n 13

Neal J. Weinreb, M.D., FACP
Regional coordinator, southeast
International cooperative Gaucher group
Director, University Gaucher treatment center, Tamarac, Florida

Experts in medical genetics often talk about a "founder effect." This refers to a genetic trait or disease that has a high frequency in a contemporary population, because the gene was introduced by a founder into a small, often geographically or socially isolated group of people whose numbers then rapidly expand.

Medical Research and Practice Updates

GAUCHER DISEASE
IN ASHKENAZIC JEWS

For hundreds of years, the Ashkenazic Jews of Germany and middle and eastern Europe experienced sudden periods of population contraction (Crusades, pogroms, holocaust) followed by concentration in restricted areas (ghettos, Pale of Settlement) where, like their ancestors in Goshen, the Jewish people temporarily multiplied to large numbers. It is therefore not surprising that the Jewish people, when dispersed and scattered, and dwelling in small, isolated pockets among foreign nations, has become susceptible not only to assimilation and persecution, but also to a variety of hereditary genetic illnesses. Without any thought of exonerating the assailants, theologians might interpret the history of Ashkenazic Jewry not as the "founder effect," but rather as the "Founder" effect recounted in the Torah as the price to be paid for sins of rebellion and senseless hatred. "The L-rd will multiply plagues to afflict you and your descendants with severe recurring illnesses, pernicious persistent sickness." (Deuteronomy 28:59) The Biblical commentator Rashbam comments on the word *ne'emanim*: prolonged, self-perpetuating, from generation to generation. This surely must refer to genetic disease!

In 1894, the Dreyfus affair shook the Jewish world and put to permanent rest the illusion that western culture could suppress that most intractable of hereditary, psychosocial diseases, namely anti-Semitism. Subsequently, and within our lifetimes, the Jewish people have suffered all of the pain and suffering depicted in the Biblical admonitions. Contemporaneously, we have also identified a number of hereditary, genetic disorders that are particularly prevalent in various Jewish sub-populations. Among Ashkenazic Jews, the most common is Gaucher disease (pronounced go-shay) which, coincidentally or otherwise, was first described in Paris, in 1882, just twelve years before Dreyfus.

What is Gaucher disease?

Gaucher disease is named for the young French medical student who first described the disorder (which he mistook for a malignancy) in a 32 year old woman with an enlarged liver and spleen. Nearly half a century elapsed before the true nature of Gaucher disease as a metabolic storage disorder began to be understood. In 1934, a complex, fatty substance called glucocerebroside was isolated from the swollen spleen of a Gaucher patient. In 1965, my mentor, Dr. Roscoe Brady and his co-workers proved that the accumulation of glucocerebroside is due to the hereditary deficiency of a single essential enzyme called glucocerebrosidase.

What's so important about glucocerebrosidase?

Specific cells in the body called macrophages remove worn-out cells and other unwanted debris by degrading them to simple molecules for recycling. This digestive process takes place in a cell compartment called a lysosome. The enzyme glucocerebrosidase is 1ocated within lysosomes, and is responsible for breaking down glucocerebroside which comes from membranes of senescent red and white blood cells. People with Gaucher disease lack the normal form of glucocerebrosidase, and are unable to digest glucocerebroside, which then accumulates within the macrophage. The enlarged, swollen macrophages, engorged with the undigested fatty material, have a characteristic microscopic appearance. They are called Gaucher cells, and for many years, the diagnosis was dependent on finding these hallmark cells in the liver, spleen, and bone marrow. As more and more Gaucher cells accumulate, they crowd the normal liver, spleen and bone marrow cells, leading to swelling of organs, disruption of the bone marrow and of the blood cells normally produced therein, and contribute to the destruction of the bones that house the diseased marrow.

How is the body affected?

Although Gaucher cells may be in any organ, they are most numerous in those body organs in which macrophages are most active: the liver, spleen, bone marrow, and lungs. In Type I Gaucher disease, which is the most common variant, the brain is not involved and neuromental development is normal. Types II and Ill occur much more rarely, and to no greater extent among Jews than among the general population. Both these variants are associated with neurological deterioration and dysfunction. Type II disease, also referred to as the infantile variant, is particularly devastating and invariably fatal within the first two years of life. Although reminiscent of Tay-Sachs disease, it is unrelated.

Even with the more commonly encountered Type I Gaucher disease, which may be present in as many as one in every 6oo Ashkenazic Jews, patients differ greatly as regards the age of onset and severity of symptoms. We don't fully understand the reason for this variability, which can be striking even among affected siblings. We know that Gaucher disease is associated with a number of different genetic mutations and that the type of mutation does, to some extent, influence the physical manifestations of the disease. However, even among people with the same genotype, the clinical picture can differ dramatically.

The following describes some typical cases. There is Rivka who, when 3 years old, is found to have a large liver and spleen by the pediatrician. By age 6, she's very small for her age, and has a large protuberant belly, spindly arms and legs, and multiple bruises. Kids give her a hard time because she's always too tired to play and she looks weird.

Consider the case of 11 year old Reuven and his 15 year old brother, Shimon. Reuven looks a lot like Rivka, and isn't much taller. He misses lots of school days because his arms and legs always hurt. Shimon, since his Bar Mitzvah, has been in the hospital twice with high fever and severe excruciating pain in a red, swollen leg (a bone crisis). Yaakov has had aseptic necrosis, or bone death, of both hips, and walks with a marked limp.

Rachel, now 29 years old, had delayed onset of puberty and repeated severe nosebleeds. In 1981, her spleen was removed. The bleeding stopped, but she then developed collapse of the hips and had unsuccessful hip replacement surgery. She now spends most of her time in a wheel chair and has never had children.

On the other hand, Dina had a splenectomy during her first pregnancy. She delivered uneventfully and has two other children. However, at age 36, she fractured her distal femur near the knee. Repeated surgery and attempted knee replacement failed because of the development of chronic infection, and her knee continues to drain. She gets around on crutches, and is a very successful counselor for abused women.

Fifty-two-year-old Dr. Shtarker who learned that he had Gaucher disease when he failed his army physical. Although his bone x-rays were abnormal, he always insisted he felt fine, until he fell playing racquetball and fractured his thigh.

Mrs. Miltz first found out she has Gaucher disease at age 65. Her spleen is slightly enlarged, but except for aches and pains that she blames on arthritis, she feels great.

Mr. Eli was also in his late 60's when he was diagnosed. His platelet count was quite low, but he changed little over ten years of observation. One day, on his way to a card game, he tripped and fell on his head. He began to bleed around the brain and was taken to surgery. Because the neurosurgeon couldn't stop the bleeding, he had an emergency splenectomy. Unfortunately, although his blood counts are now normal, Mr. Eli never regained full mental acuity, and is now in a nursing home.

Finally, there is the case of Moshe, who made a point of never

going to the doctor. At age 80, he developed a mild speech problem, which the doctor attributed to a large hemangioma of the lip. Serendipitously, he was found to have a slightly enlarged spleen and Gaucher disease was diagnosed. His blood counts are barely abnormal, and he continues fully active as a condo politician and senior handball champion.

In truth, every individual Gaucher patient has a unique story. Given the degree of clinical variability, it should not be surprising that the management of Gaucher disease presents a significant challenge in diagnosis, prognosis, and treatment. In fact, we suspect that there are significant numbers of Ashkenazic Jews with Gaucher disease who are yet to be diagnosed. This is why it is so important to recognize the symptoms of Gaucher disease. These symptoms include fatigue, easy bruising and bleeding, bone pain, bone fractures, enlarged spleen and liver.

How do you get Gaucher disease?

Gaucher disease is an inherited disorder, passed on from parents to children by the transmission of an abnormal gene. Genes contain the blueprints that the body's cells use to produce proteins and enzymes. An individual normally inherits one copy of each gene from each parent. Therefore, each cell contains two genes capable of directing the production of an enzyme such as glucocerebrosidase. In an inherited, recessive disorder such as Gaucher disease, if a person is endowed with at least one normal gene, from either parent, that person will manufacture sufficient enzyme to lead a perfectly normal life. However, that healthy person with one normal and with one abnormal gene can still pass that abnormal gene to his children. That is why such an individual is called a "carrier."

Should two carriers marry and have children, there is a 25% chance that a child will have Gaucher disease. There is also a 25% chance that the child will be normal and have two normal genes. The odds are 50% that the child will be another carrier. Remember, though, that we are discussing probabilities. In real life, it's possible, but unlikely, three children in a row could have Gaucher disease. The more children one has, of course, the greater is the likelihood that the distribution will approach the predicted proportion.

If a carrier marries someone with Gaucher disease, the odds of having a Gaucher child rise to 50%. In this marriage, all the children who do not have Gaucher diseases will be carriers. On the other hand, if a carrier marries a genetically normal person, no child will be born with Gaucher disease, but 50% of the children will likely be carriers. Should two Gaucher patients marry and have children, all will be born with Gaucher disease.

How many people have Gaucher disease?

Although Gaucher patients may be found among all ethnic and racial groups, it is very rare in the general population, occurring in fewer than one in 50,000. Among Ashkenazic Jews, however, the frequency is much greater. As many as one in every 600 Ashkenazic Jews is believed to have some form of Gaucher disease, and the frequency of the carrier state may be as great as one in 15-20, far greater than that of Tay-Sachs disease. Does that mean that we should encourage mass screening programs for Gaucher disease similar to those which have been so successful in combating the transmission of Tay-Sachs? Most geneticists think not, especially because Type I Gaucher disease is almost never fatal at an early age and is often compatible with a long and productive life. Furthermore, unlike Tay-Sachs disease, an effective treatment is available for symptomatic Type I Gaucher patients. However, it is advisable for family members and relatives of known Gaucher patients to be tested for carrier status. A simple blood test is all that is required. Appropriate diagnostic tests for Gaucher disease should be offered to all relatives of Gaucher patients who have clinical findings that are associated with Gaucher disease.

How is Gaucher disease diagnosed?

Diagnosing Gaucher disease is not always straightforward as some symptoms may resemble other diseases such as arthritis or even leukemia. When Gaucher disease is suspected, the diagnosis can be established by a blood test showing a decreased activity level of glucocerebrosidase in white blood cells. Nowadays, it is rarely necessary to require a bone marrow sample purely for diagnostic purposes. Diagnostic testing for Gaucher disease is easily available throughout the United States, Israel, and Western Europe. For further information about Type I Gaucher disease treatment centers, Gaucher Disease, or its treatment, please refer to www.gaucherdisease.org.

Dr. Neal Weinreb has been caring for patients with Gaucher disease for 33 years. He is a member of the Young Israel of Hol1ywood-Ft. Lauderdale, Fla. and has discussed Gaucher disease at the annual International Jewish Medical Ethics Conference. **He can be contacted at www.gauchersoutheast.com.**

Yael Oppenheim and Terry F. Davies

Division of Endocrinology, Diabetes and Bone Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, New York.

Supported in part by: NIH grants DK52464, DK35764 and DK45011 and the David Owen Segal Endowment.

Hyperthyroidism implies thyrotoxicosis due to excess thyroid hormone secretion from the thyroid gland rather than any other source. It may vary from a mild subclinical disorder to a serious life-threatening medical condition in which a patient's thyroid hormones are greatly elevated.

Medical Research and Practice Updates

HYPERTHYROIDISM
TREATMENT STRATEGIES

Hyperthyroidism is found more often in women than men and studies have suggested a population prevalence of approximately 2 percent of women and 0.2 percent of men (1). Clinically, hyperthyroidism is characterized by symptoms such as anxiety, weight loss, sleeplessness, diarrhea, palpitations, sweating and heat intolerance. There are a variety of treatment modalities for hyperthyroidism and their applications can vary based on physician and patient acceptance of the evidence available. Furthermore, there are still distinct national and international patterns of treatment for this condition (2). While the decision to treat with a particular therapy depends considerably upon the underlying pathology, the various options available remain medical therapy, radioactive iodine and surgery.

Medical Therapy of Hyperthyroidism
Advantages and disadvantages

The advantages of medical therapy include a high response rate, low cost and the lack of thyroidal destruction. The disadvantages of medical therapy include variable compliance, high relapse rates after discontinuation (60%) and serious drug reactions (2). The most commonly used antithyroid drugs are the thionamides (methimazole and propylthiouracil), iodine, and corticosteroids.

Thionamides. Mechanisms of Action:

Thionamide drugs inhibit thyroid hormone synthesis but have no direct effect on thyroid hormone release or iodide uptake. The thionamides most commonly used in clinical practice are propylthiouracil (PTU) and methimazole (MMI) (or its precursor carbimazole). PTU, but not MMI, also inhibits peripheral deiodinase activity, although this advantage is usually not achieved at traditional dosing used to treat hyperthyroidism (2). Both drugs also appear to have immune suppression activity via a local action on the immune infiltrate or by inhibiting thyroid antigen production (2). For example, methimazole has been shown to induce apoptosis of the invading T cells via the Fas-FasL system (3).

Dosing: Methimazole has a much longer half life (3-5 hrs) than PTU (1-2 hrs) and it has been well shown that MMI can be given once a day whereas PTU needs to be dosed 2-3 times a day to maintain thyroid blockade (1, 4) . The usual starting dose should be based on the degree of excess thyroid function but typically need not exceed 20mg of MMI or 300mg of PTU. After 4 to 6 weeks, the dose of the applicable thionamide is adjusted based on thyroid functions and clinical symptoms. Maintenance dosing is usually 5 to 10 mg per day of MMI and 100 to150

mg per day of PTU (1). Most patients become euthyroid after 6-12 weeks of therapy. This time frame can vary depending on gland size, severity of the disease as assessed by TSH receptor antibody levels and extrathyroidal manifestations of the disease, drug timing and drug dosing (4).

Thionamide Choice - PTU vs. MMI: There is no clear consensus among physicians regarding the use of PTU versus MMI. Data suggest that MMI is less associated with fulminant hepatitis and other major side effects, and is easier for patients to take as it is dosed once daily and in much lower concentrations (4). Accordingly, we prefer MMI in most cases except in accelerated hyperthyroidism where the peripheral effects of PTU may be theoretically helpful, and in pregnancy where PTU has had less side effects (see below).

Side effects of thionamides: Reactions to thionamides have been reported in approximately 5% of patients and these side effects may be dose related or idiosyncratic. The most common toxicities include hypersensitivity reactions and bone marrow effects, the most serious - agranulocytosis - being see in up to 0.5% of patients. Hypersensitivity reactions, which can include rash, pruritis, urticaria, fever, arthralgia and serum sickness, tend to resolve after discontinuation of thionamides (2). Bone marrow toxicities include leukopenia, thrombocytopenia, anemia and bone marrow aplasia. The development of agranulocytosis is idiosyncratic. Patients on thionamides who develop signs of infection (fever, flu-like symptoms, sore throat, malaise, generalized aching, rash, pruritis) should immediately stop the thionamide and have a complete blood count drawn.

Severe bone marrow suppression: Patients with leukocyte counts <2000/mm3 or granulocyte counts <1000/mm3 should be admitted to the hospital, placed in isolation, and treated with intravenous fluids and antibiotics. The treating physician should consider administration of granulocyte colony stimulating factor (GCSF) if the white blood cell count does not rise after discontinuation of the thionamides. The GCSF can be stopped once the white count normalizes. The re-administration of thionamides is contraindicated in these patients (2).

Other systemic toxicities: Although rare, these include a polyarthritis syndrome (skin eruption, arthralgia, arthritis, fever and myalgia), polymyositis, hepatic insufficiency, toxic hepatitis, vasculitis, liver failure, Mikulicz's syndrome (bilateral salivary and lacrimal inflammation), edema, disseminated intravascular coagulation, rhinitis, conjunctivitis, lymphadenopathy, diarrhea, alopecia, loss of taste and hypoprothrombinemia (2). The toxicity of hepatic failure deserves further comment as it can be particularly life threatening. Therefore, periodic liver function testing is recommended although the liver dysfunction may not be predated by detectable liver function abnormalities. Any patient on thionamides who develops signs or symptoms of hepatic failure (nausea, vomiting, diarrhea, jaundice, abdominal pain) should immediately stop the medication and have a full set of liver functions evaluated. MMI is more classically associated with cholestatic hepatitis whereas PTU is more regularly associated with severe fulminant hepatitis. Younger patients appear to be more at risk for severe hepatitis (4). While patients who have had minor reactions to one thionamide can be started on an alternate thionamide under close observation, patients who have experienced hepatitis, immune suppression or vasculitis from a thionamide should never be re-challenged, even with an alternate thionamide (4).

Treatment Outcomes: It is our opinion that patients with Graves' disease should undergo a trial of thionamide therapy for at least six to twenty-four months. Data about the cure rate for Graves' patients on thionamides is conflicting, ranging from 10 to 75 percent and likely to be dependent on the level of iodine intake in the population under study (1). Other factors that are correlated with risk of relapse are patient age, male sex, pregnancy, large goiter, smoking, high T4 & T3 levels at diagnosis, TSH-receptor antibody levels prior to withdrawal, and more than one prior course of failed treatment. Combined thionamide and levothyroxine therapy has been suggested to decrease the remission rate but evidence argues against the effectiveness of this strategy (4).

Anti-adrenergic agents (ie: propanolol)

Beta adrenergic blockers may be given for symptomatic relief in patients with moderate or severe symptoms. These drugs inhibit sympathetic activity but do not disturb thyroid hormone release although inhibition of deiodination has been reported. A useful starting dose is propranolol 20 mg qid. In general, beta adrenergic blockade should not be used as solo therapy except as pre-treatment for surgery or radioactive iodine.

Iodides (Stable Iodine I127or Lugol's iodine or SSKI)

Iodides are used to control hyperthyroidism when rapid stabilization of thyroid function is desired. They are also used for pre- treatment for surgery and sometimes as post treatment for

radioactive iodine therapy. Large doses of iodine must not be given to patients who are scheduled to receive radioactive iodine within the next several weeks as iodine loading inhibits thyroidal uptake of the radioactive iodine.

Mechanism of action: Iodine inhibits organification and release of thyroid hormone and inhibits thyroid cell growth. However, in iodine depleted hyperthyroid patients, iodine can actually worsen the hyperthyroidism and should, therefore, be avoided in this population. The response of diseased glands to chronic iodine administration is unpredictable and many patients will escape from its effects, a phenomenon known as the Wolff-Chaikoff effect. Chronic iodine use is, therefore, not recommended.

Side effects: These are primarily hypersensitivity reactions, which are mostly dose related and resolve with discontinuation of the drug (2).

Corticosteroids (prednisone or dexamethasone)

Corticosteroids are indicated in severe hyperthyroidism, when rapid control of disease is necessary. Other indications for steroids in the treatment of hyperthyroidism are to prevent the progression of thyroid orbitopathy, including patients receiving radioactive iodine, and in the treatment of painful subacute thyroiditis.

Mechanism of action: Corticosteroids decrease thyroid hormone secretion and peripheral monodeiodination. Part of this action is via their immunosuppressive action inducing apoptosis of lymphocytes resulting in rapidly falling levels of TSH-receptor antibodies.

Side effects: Short term steroids have multiple potential side effects including possible dyspepsia, unmasking an underlying type 2 diabetes, and steroid-induced psychosis. Prednisone can occasionally cause edema and a hypokalemic acidosis and should, therefore, be avoided in patients with severe high output cardiac failure (2).

Other antithyroid drugs

Lithium: Lithium is occasionally used in the treatment of hyperthyroidism in conjunction with thionamides. This is most commonly helpful in patients who cannot tolerate iodine. It has also been advocated for pre and post radioactive iodine ablation and surgery. Lithium's mechanism of action is to inhibit thyroid hormone release in the same way as iodine. It has also been shown to have a toxic effect on lymphocytes. The clinical side effects of lithium are multiple and can occur at both therapeutic and toxic levels. The most severe side effects can include coma, stupor, renal disease, neurological problems and cardiac arrhythmias. Lithium has been reported to worsen Graves' orbitopathy, which improves with withdrawal of the drug. The use of lithium to treat hyperthyroidism is limited by these potential side effects (2).

Oral Cholecystographic Agents: The oral cholecystographic agents used in the treatment of hyperthyroidism include sodium ipodate and sodium iopanoate (4). These agents blocks monodeiodinase activity and thyroid hormone secretion (5). The usual dosing of these agents is 1 gram daily or 500 mg twice daily (4). Sodium ipodate is no longer commercially available in the United States (5). The use of the oral cholecystographic agents is limited mainly by their large iodine content, which delays the ability to treat with radioactive iodine and may actually aggravate the hyperthyroid condition. These agents cannot be used as long-term solo therapy as many patients escape from the inhibition - just as they would from iodide. The primary indication for these agents has therefore been their speed of action. Indeed, some investigators have claimed them to be quicker than the iodides themselves. They may also be helpful in cases where conventional therapy is ineffective or contraindicated (2,5).

Other drugs: These include non-steroidal anti-inflammatory drugs, salicylates and COX-2 inhibitors to treat painful subacute thyroiditis, Bile acid sequestrants bind thyroid hormone in the gut and can be used to manage iatrogenic and factitious hyperthyroidism and octreotide, dopamine receptor agonists, and 3,5,3'-triiodothyroacetic acid (TRIAC) have all been used to treat TSH dependent hyperthyroidism.

Radioactive iodine use in hyperthyroidism

Advantages and disadvantages: Radioactive iodine is simple to administer, safe and predictable and has low costs. The important disadvantages are the potential need for lifelong thyroid hormone replacement therapy, the possible requirement for more than one treatment dose, and the regulatory requirements surrounding its use. Radioactive iodine can also induce a radiation thyroiditis, which peaks at 10 to 14 days. This radiation thyroiditis can be quite painful and may worsen the hyperthyroid symptoms and even precipitate arrhythmias in susceptible patients.

Indications: In order for radioactive iodine to be effective, patients must have an adequate radioactive iodine uptake. Candidates for radioactive iodine include patients who have hyperthyroid