A Limp Left Lung

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While "on call" one night in the QEII radiology department the following radiograph **(see Fig. 1 and Fig. 2)** is brought to you by one of the technologists . Inside, the requisition gives the following information:

45 yr. old female with hx of renal tumor, now dyspnea x2 wks

Previous films taken 8 months ago (not shown) appear normal.

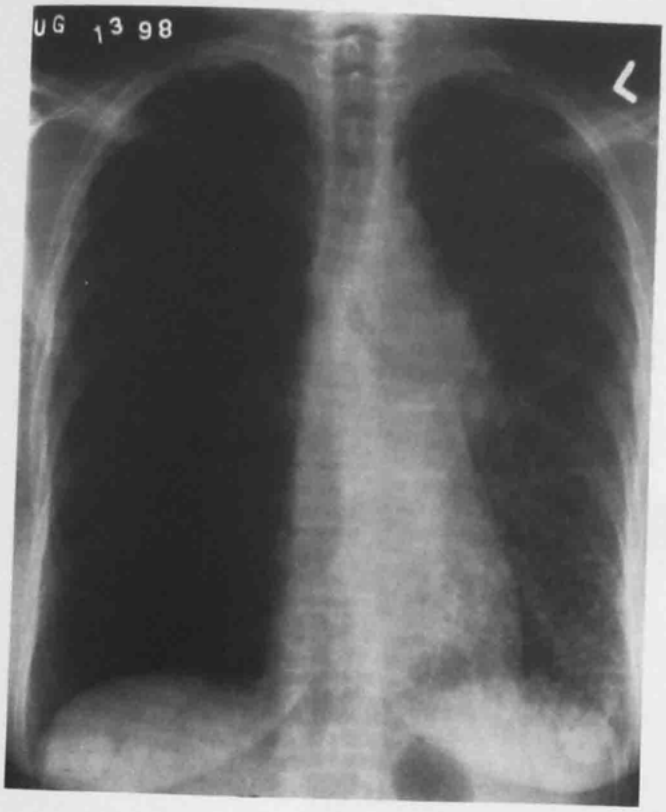

Figure 1. PA Chest

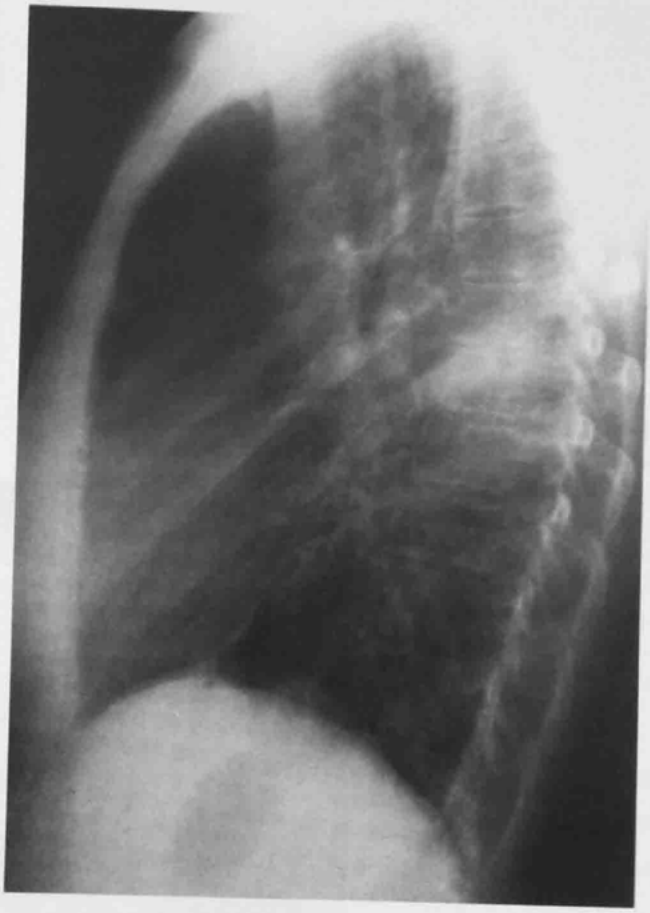

Figure 2. Lateral Chest

Q1: Can you identify the abnormalities?
Q2: Provide a differential diagnosis.
Q3: What investigations (radiological) would you recommend at this time?

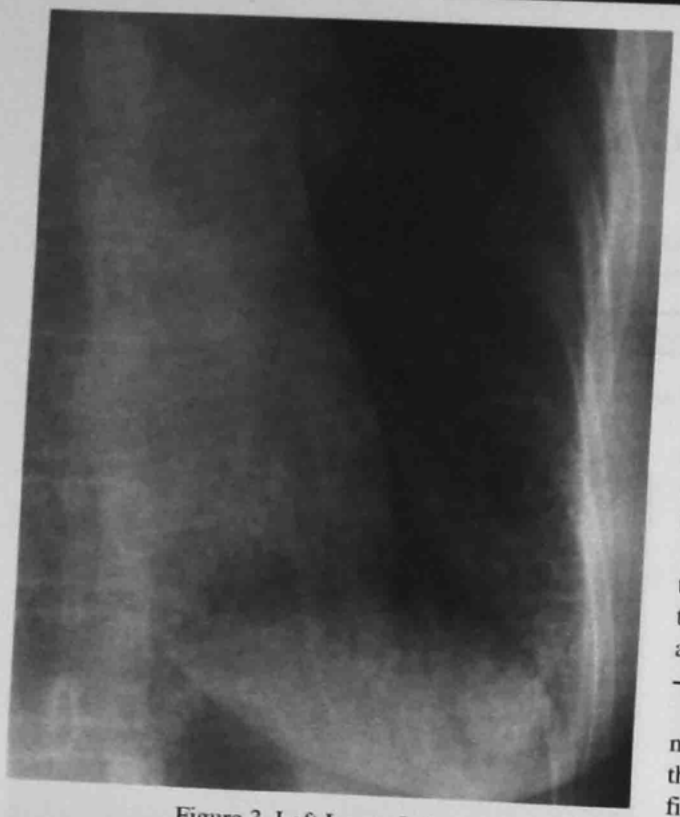

Figure 3. Left Lower Lobe

A1: The left hilum is prominent. There is opacification and abnormal convexity in the AP window*. Reticular opacities are seen in the left lower lobe. There are associated Kerley B lines‡ (**see Fig. 3**). The right lung and cardiac silhouette are normal.

A2: There are a number of possibilities for consideration. Given this patient's history of a malignancy, the primary concern should be metastatic involvement with invasion of the lymphatic system of the lung (lymphangitic carcinomatosis). A second malignancy like a bronchogenic carcinoma could give this appearance if there was local metastatic spread via the lymphatics. An atypical interstitial edema due to a localized obstruction could also present this way. Although it is not stated in the history, the patient may be on chemotherapy and therefore an opportunistic infection should also be a consideration.

A3: To resolve the above possibilities a High Resolution Computed Tomography (HRCT) would be helpful to further characterize the abnormalities. Below is a selected image from the HRCT series done on this patient (**Fig. 4**).

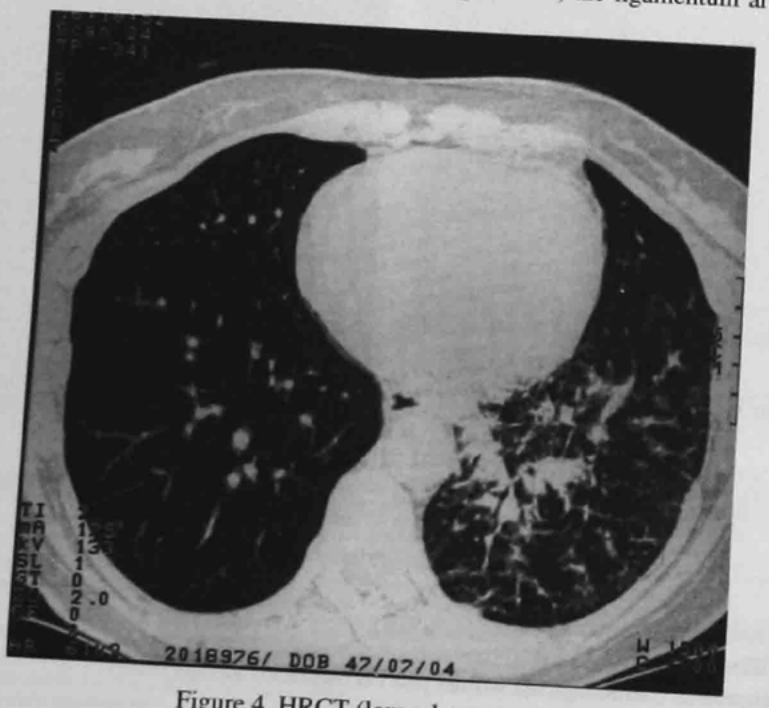

Figure 4. HRCT (lower lung zone)

Q4: Describe the findings on the images.
Q5: Does this patient need a biopsy?

* The Aortopulmonary (AP) window is a region of the mediastinum inferior to the arch of the aorta and superior to the left main pulmonary artery on the anterior-posterior chest film. It is bound medially by the lower trachea and esophagus and laterally by the left lung. In a normal subject the area is radiolucent and is usually concave in its shape. It contains lymph nodes, the ligamentum arteriosum and the recurrent laryngeal nerve.

‡ Kerley B lines appear as a result of fluid within the interlobular septa. These lines are usually short (<2 cm), horizontal lines commonly seen at the lateral borders of the lungs near the costophrenic angles.

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Abstract: The abstract should appear on the second page and should be no longer than 250 words. It should state the purpose of the paper, basic procedures, main findings and the principal conclusions.

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Chapter in book

2. Hahn JF, Mason L. Low back pain in children. In: Hardy Rw Jr, ed. *Lumbar disc disease*. New York: Raven Press, 1982:217-28. (Seminars in neurological surgery).

Book

3. Katz J. *Common orthopedic problems in pediatric practice*. New York: Raven Press, 1981:125-7.

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Diagnosis: Lymphangitic Carcinomatosis
(2° to renal cell carcinoma)

Lymphangitic Carcinomatosis (LC) is a process by which there is tumor growth and spread within the lymphatics of the lung (1). It occurs most commonly in patients with adenocarcinomas of the lung, breast, kidneys, gastrointestinal tract, prostate, and cervix (2). Less commonly, LC may be secondary to other malignancies such as sarcomas, melanomas, carcinomas of the head and neck, and thyroid carcinoma. LC usually results from hematogenous spread to the lung with subsequent interstitial and lymphatic invasion (2). In the case presented here, the patient had a nephrectomy 2 years prior to developing LC. The pathological report showed a Grade 3 Mixed Clear and Renal Cell carcinoma with no capsular involvement. Tumor invasion into the renal vein was demonstrated at the time of resection.

LC can also occur because of direct lymphatic spread of tumor. Malignancy with hilar lymph node involvement may spread through the lymphatics in a retrograde fashion. Bronchogenic carcinoma sometimes invades the pulmonary lymphatics directly and may give rise to segmental or lobar LC (3). Antegrade flow through the diaphragm or pleural surfaces is a less common mechanism of invasion (4).

The pathologic appearance for LC has been reported to include the following: i) gross thickening of bronchovascular bundles and interlobular septa, ii) fine accentuation of the pleural lymphatic network, iii) malignant cells in the lymphatic vessels, iv) tumor thrombi, and v) localized plaques of subpleural tumor (1).

While there are some characteristic features present on plain film radiographs, the findings are usually non-specific. X-ray manifestations of LC occur because of a combination of dilated lymphatics and interstitial edema, together with opacities caused by the tumor cells themselves. The appearance of fine septal lines in the interstitium may represent the earliest detectable radiographic sign of LC (5). Most often pulmonary involvement is bilateral and symmetric. However, the changes can be unilateral, particularly in cases resulting from lung or breast carcinoma. In about 50% of cases of pathologically proven LC, the chest radiograph is normal (2,3). Plain film findings are outlined in **Table 1**.

Not surprisingly, CT scanning (particularly HRCT) is more sensitive than plain film radiography in the detection of LC (1).

Table 1: Plain Film Findings of LC

1. reticular or reticulo-nodular interstitial markings (usually with irregular contours)
2. thickening of the interlobular septa (Kerley B lines)
3. hilar and mediastinal lymphadenopathy
4. pleural effusion (common)

Table 2: HRCT Findings of LC

1. peribronchovascular interstitial thickening (smooth or nodular)
2. interlobular septal thickening and fissural thickening (smooth or nodular)
3. preservation of lung architecture
4. prominence of centrilobular structures
5. lymph node enlargement and pleural effusion

A4: There is diffuse reticular opacities throughout the lower lobe of the left lung in both the peribronchovascular and interlobar regions. The lung architecture has been maintained. On other HRCT slices (not shown) enlarged lymph nodes were seen in the AP window . The HRCT findings of LC are given in **Table 2**.

A5: In a patient with a known primary tumor and a clinical history consistent with LC, typical CT findings are usually considered diagnostic and a lung biopsy is usually not performed. Without a known history of a primary tumor, further evaluation is usually necessary and CT can be helpful in selecting the most appropriate site for biopsy. Transbronchial biopsy is usually positive (2). Another diagnostic test that could be used is an open biopsy. Less invasive options include bronchoalveolar lavage, which has been used successfully in specific cases (6).

The prognosis for LC is poor. Prior to the advent of modern chemotherapy approximately 50% of patients diagnosed with LC had died within 3 months and only 15% were alive at 6 months (7). In the current era of combined chemotherapy, expected survival has increased by a few months. Regression of disease has been observed in rare cases (8). In the case at hand, the patient continued to deteriorate and developed rapid weight loss. Despite a course of palliative radiation she was eventually admitted for delirium and elevated calcium levels. The patient died approximately 3 months after the diagnosis of LC was made.

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Erratum

An error appeared on the June 1998 masthead regarding the correct title of the Medical Society of Nova Scotia. We apologize for the mistake and have corrected it on the current masthead.

Norvasc*

(amlodipine besylate/pfizer)

Brief Prescribing Information
NORVASC
(amlodipine besylate)
Tablets 2.5, 5 and 10 mg
Antihypertensive-Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY
NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

INDICATIONS AND CLINICAL USE

Hypertension
NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension.
NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of NORVASC with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.

Chronic Stable Angina
NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS
NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS

Increased Angina and/or Myocardial Infarction
Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow Obstruction (Aortic Stenosis)
NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Impaired Hepatic Function
There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).

Beta-blocker Withdrawal
NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS

Use in Patients with Congestive Heart Failure
Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that NORVASC had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.

Hypotension
NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Peripheral Edema
Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Use in Pregnancy
Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers
It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, NORVASC should not be given to nursing mothers.

Use in Children
The use of NORVASC is not recommended in children since safety and efficacy have not been established in that population.

Use in Elderly
In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

Interaction with Grapefruit Juice
Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.

Drug Interactions
As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme.
Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.
Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.
Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.
Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.
Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.
Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:
- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin.**
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Antacids
Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.
Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

ADVERSE REACTIONS
NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity.

Hypertension
In the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):
Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).

Angina
In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).
The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):
Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).
NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.
The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.
Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, increased sweating. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura.
†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.
The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.
Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms
Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment
Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION
Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.

Use in the Elderly or in Patients with Impaired Renal Function
The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).

Use in Patients with Impaired Hepatic Function
Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS

Availability
NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE
Store at 15-30°C. Protect from light.

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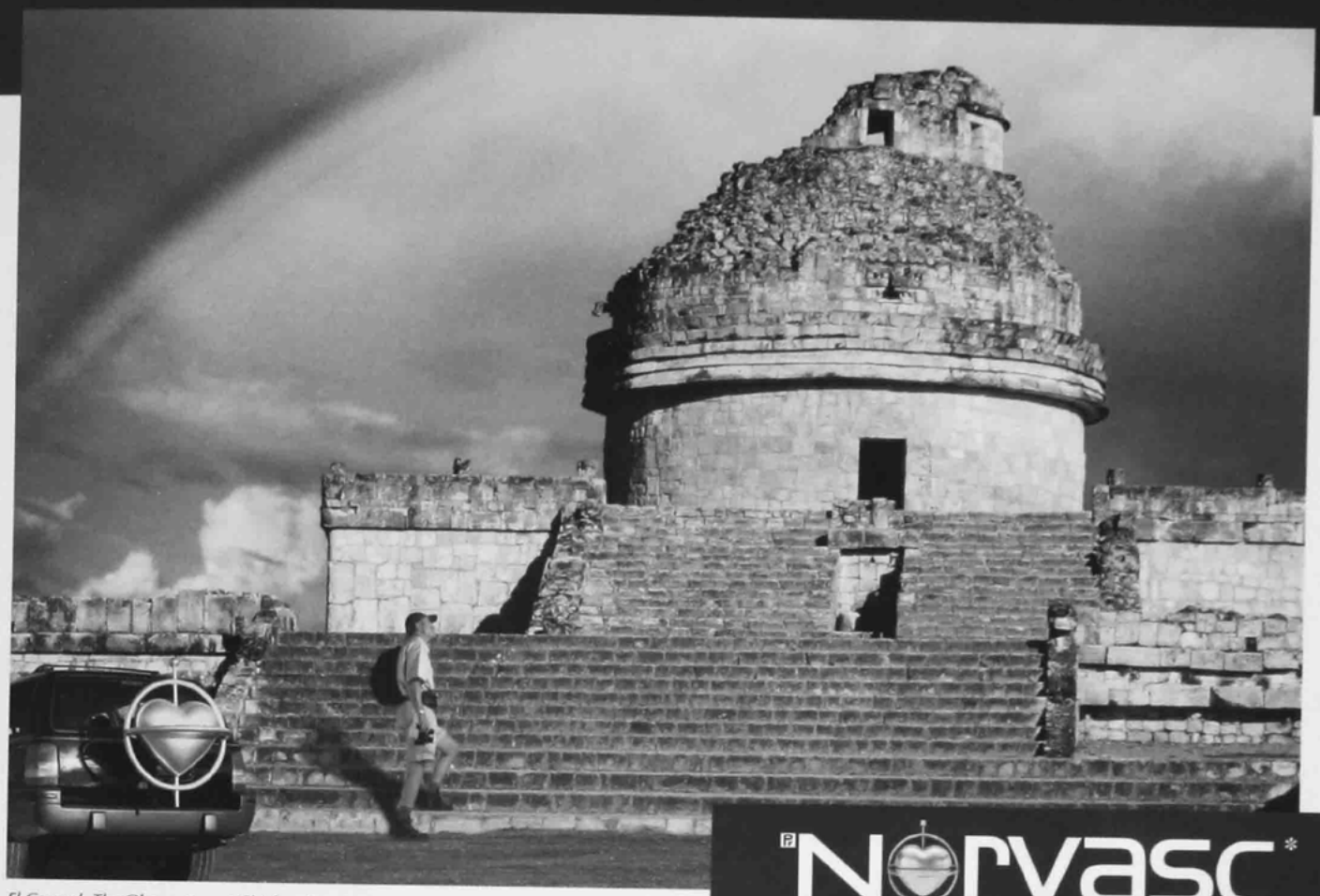
A Solid Sense Of Security In Angina. Day After Day.



El Caracol, The Observatory at Chichen Itza, Mexico

℗Norvasc*
(amlodipine besylate/pfizer)
FOR ANGINA

Broad cardiovascular safety profile

- demonstrated safety profile
  - no negative inotropic effects on the heart[1,2]
  - low potential for drug interactions[1,3]
- can be used safely in combination with beta-blockers[1‡]
- no other CCB can make this statement in their product monograph[1]:

  "although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that Norvasc* had no overall deleterious effect on survival and cardiovascular morbidity in short-term and long-term clinical trials in these patients"

Effective relief of angina symptoms

- effectively reduces the frequency of angina attacks[4,5]
- as effective as diltiazem SR in relieving angina symptoms[6†]
- proven effective in hypertension and angina[1]

‡ When beta-adrenergic receptor blockers are administered concomitantly with amlodipine, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

† Norvasc* 5-10 mg o.d. (n=66) versus diltiazem 90-120 mg b.i.d. (n=66) after 8 weeks (p=ns).

Norvasc* is indicated for the management of chronic stable angina in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.

The most common adverse reactions include edema (9.9%) and headache (7.8%).[1]

Consult prescribing information for important safety information and drug interactions.

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Pfizer
We're part of the cure

HERE TODAY. HERE TOMORROW.

The body of evidence continues to grow for triple therapy in CHF.

PrLANOXIN® in combination with an ACE inhibitor and diuretic (triple therapy) proves more beneficial than dual therapy** (ACE inhibitor and diuretic) **in CHF*

HELP REDUCE YOUR CHF PATIENTS' CHANCES OF COMING HERE

- *Reduced risk of hospitalization due to worsening heart failure*[1]
- *Delayed progression of disease in mild to moderate CHF*[2]
- *Improved feeling of general well-being with fewer symptoms*[2]
- *Greater exercise tolerance and endurance*[2]
- *Proven safety profile*[1†]

*DIG study: 6,800 patients with mild (68%), moderate (30%), or severe (2%) CHF.[1] RADIANCE study: NYHA Class II-III CHF.[2]
†Only 2% hospitalized for suspected toxicity in the digoxin group vs. 1% in the placebo group. Suspected toxicity was 11.9% in the digoxin group versus 7.9% in the placebo group. Among these patients, 16.5% in the digoxin group were hospitalized versus 11.4% in the placebo group.[1] Overall in clinical trials only 1-4% of patients experienced adverse reactions considered serious.[3]
Digoxin dosage should be individualized and based upon clinical assessment of each patient.[3]

PrLANOXIN®
digoxin

A classic therapy improving today's health outcomes in CHF

GlaxoWellcome

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