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Update in Internal Medicine

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Abstract

More than 500,000 new medical articles are published every year and available time to keep updated is scarcer every day. Nowadays, the task of selecting useful, consistent, and relevant information for clinicians is a priority in many major medical journals. This review has the aim of gathering the results of the most important findings in clinical medicine in the last few years. It is focused on results from randomized clinical trials and well-designed observational research. Findings were included preferentially if they showed solid results, and we avoided as much as possible including only preliminary data, or results that included only non-clinical outcomes.

Some of the most relevant findings reported here include the significant benefit of statins in patients with coronary artery disease even with mean cholesterol level. It also provides a substantial review of the most significant trials assessing the effectiveness of IIb/IIIa receptor blockers. In gastroenterology many advances have been made in the *H. pylori* eradication, and the finding that the cure of *H. pylori* infection may be followed by gastroesophageal reflux disease. Some new antivirals have shown encouraging results in patients with chronic hepatitis. In the infectious disease arena, the late breaking trials in anti-retroviral disease are discussed, as well as the new trends regarding antibiotic resistance. This review approaches also the role of leukotriene modifiers in the treatment of asthma and discusses the benefit of using methylprednisolone in patients with adult respiratory distress syndrome, among many other advances in internal medicine.

Keywords

Review; Meta-Analysis; Clinical trials; Internal medicine; Medical education

Introduction

Two years ago, *Archives of Medical Research* published the review article entitled Frontiers of Internal Medicine (1). As an initial effort to gather and review the most relevant findings applicable to clinical practice, it was warmly welcomed. Many reprints were requested from readers in more than 25 countries on four continents.

At the velocity of about 500,000 new medical references every year, the task of selecting useful, consistent, and relevant information for clinicians must continue. On this occasion, we included important areas that were not represented last time, such as rheumatology, gastroenterology, oncology, and behavioral medicine.

This review focuses on results from randomized clinical trials or from well-designed observational research. Also, a great effort was made to include only articles with solid results, avoiding seduction by preliminary data. Most of the information provided here targets clinical outcomes such as survival, quality of life, or improvement of symptoms. Results based only on surrogates were excluded because their clinical meaning is often unclear. Additionally, authors whose articles are included here have no monetary conflict of interests. Therefore, readers may be confident that there is no economic bias either in the selection of articles or in their interpretation.

Clinical Epidemiology

The process of gathering, analyzing, and applying scientific and clinical data to everyday clinical practice marches on. Each year, more and more publications include topics related to clinical epidemiology aimed at clinicians. Physicians are increasingly familiar with concepts such as pre-test probability, positive predictive value, and the number needed to treat to prevent an event. Furthermore, clinicians incorporate these concepts into their clinical decision making. Meta-analysis or systematic reviews now substitute for the opinions of experts, and journals now tend to include case reports only if they represent a singular teaching case and not only whether they are based on the rarity of the event.

Evidence-Based Medicine

Clinical knowledge based on well-designed clinical research is at present considered more valuable than anecdotal facts, untested experience, or research performed on animals. Although evidence-based medicine does not represent a scientific paradigm, it does constitute a process to obtain clinical knowledge that fulfills the requirements to be considered scientific (2). A philosophy originally limited to general internal medicine practitioners, evidence-based medicine now extends to areas such as surgery, obstetrics, and psychiatry.

The practice of evidence-based medicine will have a significant impact particularly on developing countries with limited budgets. It is justifiable for any country with endless needs and scarce resources for health to focus on interventions with proven benefit on survival or quality of life.

Challenges in Clinical Trials

The cornerstone of clinical epidemiology and evidence-based medicine is the randomized clinical trial. It is considered the gold standard to test the efficacy of a medical intervention.

With the overwhelming number of clinical trials published or ongoing in almost all disciplines of medicine, the limitations of clinical trials are now even more evident.

Patient selection constitutes a major problem. Subjects usually have no significant co-morbidities. They tend to be compliant and many are followed in academic institutions. These patients are far from being representative of the bulk of the population. It is possible that interventions with marginal benefit in clinical trials would have no beneficial effect when performed in unselected patients or under real-life conditions.

Another challenge for randomized clinical trials is to define a clinically significant benefit. Currently, a medical intervention is considered beneficial if it shows an absolute reduction in mortality as low as even 3%. Statins became the gold standard of treatment for patients with hypercholesterolemia because they increase the likelihood to be alive at 6 years from 88 to 91% (3). While clinical trials target populations at lower base-line risks, and as they enroll larger numbers of patients, the chance to find minuscule clinical benefits is high. When side effects are frequent or severe, minimal clinical benefits are obviously unjustified. However, in cases with low complications attributed to the intervention, the definition of significant benefit may become an ethical, economic, or cultural issue.

Meta-Analysis

It is not uncommon to have several clinical trials or observational studies assessing the same question under quite similar circumstances, with opposite findings. When this happens, clinicians may become even more confused than before any results were published. Meta-analyses, also known as systematic reviews, are intended to help when this occurs.

Sometimes, lack of statistical significance is due to the limited number of patients enrolled. In this case, discrepancy among studies is more likely to be resolved when data are pooled. However, in many situations, discrepant results are the consequence of differences in methodology, patient population, or study design. In those cases, the interpretation of a meta-analysis is limited.

The rules for performing a good meta-analysis are very strict, complex, and require time-consuming analyses. Many meta-statistics have been designed to assess the appropriateness of the analysis before making judgments of the results (4). Recently, strong criticism against meta-analysis of observational data has arisen as a consequence of their poor performance in predicting results in large randomized clinical trials (5).

Although meta-analyses have many limitations, their objectivity still far outweighs ignorance. Results from well-performed meta-analyses may be used as a source of preliminary evidence when they pool the results of small clinical trials, or as a source of more definite knowledge when they combine data from many large, randomized clinical trials.

Behavioral Medicine

Behavioral scientists intervene with patients within medical treatment settings to reduce factors that increase disease risk, lessen the encumbrances of illness, and promote recovery and rehabilitation via the modification of behaviors and/or psychosocial environment of the individual. This article will explicate the role of behavioral interventionists within health care settings, as well as recent advances within the field of behavioral medicine.

Social Stressors and Health

Research indicates that stress associated with social environmental factors affects the health status of individuals (6). Social stressors include stressful life events, occupational environment

characteristics, and lack of social resources, or social isolation. For example, traumatic naturalistic events, such as earthquakes and hurricanes, can precipitate myocardial infarction (MI) and sudden cardiac death in at-risk persons (7). In addition, chronic occupational stress increases the risk for coronary heart disease (CHD), hypertension, and stroke (8). Social isolation contributes to poorer prognosis in diverse medical populations (9). Behavioral interventionists work with patients within health care settings to ameliorate the impact and potential adverse physiological and/or immunological consequences of social environmental stressors.

Psychosocial Risk Factors

Research has determined that behavioral characteristics of individuals promote hypertension and related alterations in cardiac structure and function, exacerbate atherosclerosis, precipitate cardiac arrhythmias, mitigate hemostatic and thrombolytic processes, and induce myocardial ischemia in persons with CHD (10). Risk-related psychological factors include personality traits, mood disturbances, and physiological responses to stress. Risk-related social factors include low socioeconomic status and deficits in social resources.

Psychological Factors

The hostile attitudes of cynicism and mistrust toward others factor out of the Type A behavior pattern (which includes competitiveness, time urgency, and hostility) as a risk factor for CHD-related mortality (11). Psychologists facilitate the development of stress management techniques with these patients. Clinical depression is highly prevalent among individuals who survive MI and predicts additional clinical events, including re-infarction, cardiac arrest, and mortality, independently of disease severity (12). Depressed individuals also demonstrate increased risk for stroke. Further, women with a history of mental health disorder, and especially depression, demonstrate an elevation in the incidence of sudden death. Finally, the level of anxiety that a person experiences post-MI predicts subsequent arrhythmia and ischemic events, re-infarction, and sudden death. Current trials are underway to determine the effect on survival in post-MI patients treated for depression with cognitive behavioral modalities.

Hemodynamic Responses to Stress

Individuals vary in their cardiovascular responses to daily life events. Stress-induced blood pressure reactivity correlates with episodes of myocardial ischemia among CHD patients and measures of left ventricular mass (13). In addition, studies demonstrate that mental stress during daily life activities precipitates MI in at-risk populations. Mental stress appears to correlate with the extent and progression of atherosclerosis in the carotid arteries and appears to increase the risk for later clinical events among post-MI patients (14). Cognitive behavioral stress management and relaxation techniques appear to effectively diminish cardiovascular responses to acute stressors.

Modification of Risk Factors of Disease

Psychologists utilize principles of behavior change and social influence, as well as knowledge-based interventions, to reduce risk behaviors associated with the development and progression of high-risk behaviors for disease. Interventions target individuals, groups, and/or communities, and range from health education to behavior modification programs, skills training, and specified modalities of psychotherapy that have been proven to be efficacious. Objectives of disease risk reduction interventions include primary and relapse prevention, smoking cessation, weight reduction, alcohol use and abuse management, facilitation of consistent physical exercise, and dietary modification.

Smoking—The majority of smokers quit on their own accord (15). However, individuals who participate in intensive smoking cessation interventions demonstrate higher success rates. Psychologists have designed multimodal smoking cessation programs for groups, which commonly result in quit rates of 20–25% at 1-year follow-up (16). These programs concentrate on relapse prevention, which addresses symptoms associated with nicotine withdrawal, or behavioral factors such as psychological stress, weight concerns, and conditioned environmental cues for smoking. Finally, the role of the physician cannot be underestimated in smoking cessation. Directives by physicians to quit smoking typically increase quit rates by 5% or greater, higher than those attained by smokers not directed to quit (17).

Physical inactivity—Randomized trials of cardiac rehabilitation exercise programs demonstrate reductions in mortality from 15–20% 3 years following enrollment (18). Behavioral scientists attribute the effects to improvements in blood pressure levels, lipid profiles, other CHD risk factors, and potentially to increased thresholds for acute precipitants of cardiac events such as physical activity and psychological stress (19). Psychologists use principles of behavior change in order to increase physical activity, and cognitive behavioral stress management to help individuals manage daily stress more effectively.

Diet—The most effective (albeit most costly) diet modification programs utilize intensive, individualized approaches. Such interventions typically facilitate reductions in serum cholesterol levels by 5–17% (20). Dietary interventions increase their efficacy when combined with weight reduction efforts, as well as when they advocate highly prescriptive and structured diet regimens combined with frequent contact with health care professionals, and elicit the active support of spouses. Psychologists utilize knowledge-based interventions and principles of behavior change to facilitate changes in diet in at-risk populations.

Obesity—Research demonstrates that weight reduction programs that combine diet, exercise, and behavioral training result in an average weight loss of approximately 20 pounds over 20 weeks, with sustained weight loss in two-thirds of persons at 1-year followup (21). Behavioral scientists have determined that successful weight reduction interventions emphasize both diet and exercise, utilize behavioral strategies that include self-monitoring of eating behavior, and include structured relapse prevention. Finally, evidence suggests that pharmacological interventions alone facilitate weight loss minimally compared with non-pharmacological interventions (22). However, medications may increase their efficacy when combined with diet, exercise, and behavior modification interventions.

Alcohol abuse—Research suggests that alcohol consumption cessation seems to reverse many of the adverse cardiovascular effects related to alcohol abuse, such as alcohol abuse-related cardiac arrhythmias, cardiomyopathies, and risk of sudden death among patients with cardiomyopathy (23). Psychologists work with individuals who abuse alcohol to facilitate abstinence, because abstinence achieved even following long-term, heavy alcohol consumption demonstrates significant reductions in blood pressure levels in hypertensive and normotensive persons.

Behavioral Approaches to Disease Management

Psychologists work within health care settings to help medical patients manage their disease, i.e., through the reduction of symptom exacerbation (such as pain) and/or the prevention of disease recurrence. They do so by promoting effective coping, adherence to treatment, and adjustment to the functional limitations often imposed by disease. For example, interventions focus on modifying psychosocial factors, such as personality, psychological stress, and social support. Research provides evidence that psychosocial interventions reduce morbidity and mortality beyond that attained by standard cardiac rehabilitation programs for CHD patients

(24). In fact, the supplementation of usual care in post-MI patients with behavioral counseling appears to lower recurrence rates by as much as 50% over 5 years (25). Moreover, preliminary evidence suggests that rigorous, multimodal programs that integrate stress management, diet modification, and exercise mitigate coronary artery atherosclerotic plaque regression. Also, stress management interventions mitigate reduced recurrence of myocardial ischemia and other cardiac events, when compared with usual care (26).

Adherence to treatment—Without consistent patient adherence, the demonstrated beneficial effects of various treatment modalities fail to yield positive outcomes. Unfortunately, regardless of the type of therapy or the treated condition, significant percentages of patients (e.g., 30–70%) fail to adhere to prescribed treatment regimens, and therefore fail to glean the optimal benefits of these medical interventions. Non-adherence typically results in failed treatment, unnecessary or imprudent intensification of treatment, costly diagnostic procedures, disease complications, additional hospitalizations, and sometimes even death. Psychologists utilize cognitive behavioral strategies to improve adherence, including the use of environmental cues to prompt patients to take medications, integrate medications into daily habits, and facilitate parental and/or partner monitoring of patient adherence. Other strategies include recruiting the support of families, spouses, or members of structured treatment groups, applying cognitive-behavioral techniques to increase motivation in patients, and facilitating educational efforts to increase communication between health care providers and patients.

This article details only with a fraction of the large body of literature within the field of behavioral medicine. Further, this article outlines a few of the various techniques that psychologists utilize to maximize patient response to medical treatment within health care settings. Currently, behavioral interventionists work closely with physicians within various health care settings throughout the U.S. and other parts of the world. This partnership manifests the potential to optimize health care treatment now and in future years.

Cardiology

Preventive Cardiology

The need to tailor the intensity of preventive therapy to each individual according to the global cardiovascular (CV) risk profile has been emphasized by both U.S. and European guidelines (27,28). This approach acknowledges that atherosclerosis is a multifactorial process, that risk factors interact extensively with each other, and that the clinician treats the whole person, not isolated risk factors. A 20% estimated risk in 10 years or projected at age 60 has been chosen as a reasonable threshold to initiate aggressive (usually with drugs) risk factor modification, particularly hyperlipidemia and hypertension. The Framingham risk score (29) provides the best available instrument for this calculation, but its validation is critical when applied to other populations.

Hyperlipidemia—The range of individuals who benefit from lipid-lowering therapy has been increased with the LIPID (secondary prevention) and AF/TexCAPS (primary prevention) trials (30,31). Both had similar average LDL cholesterol (150 mg/dL) and HDL cholesterol (36 mg/dL) entry levels, equivalent reductions in LDL cholesterol (25%), but quite different numbers needed to treat to prevent one major CV event: 24 and 49, respectively. This difference is best explained by the underlying baseline cardiovascular risk (10-year CV risk was 26% in LIPID, 11% in AF/Tex-CAPS).

Hypertension—Effective non-pharmacological prevention and treatment of hypertension has been demonstrated in recent trials. Overweight individuals with high-normal blood pressure (BP) decreased both systolic and diastolic BP with weight loss and reduced sodium intake, individually and in combination (32). Elderly hypertensive patients showed a similar

benefit with either weight loss or reduced sodium intake (33). A diet rich in fruits and vegetables and low-fat dairy foods and with reduced saturated and total fat substantially lowered blood pressure, even in the presence of stable weight and 3 g/day of sodium intake (34).

The optimal level at which blood pressure must be lowered is still unknown. The Hypertension Optimal Treatment (HOT) trial found the lowest incidence of cardiovascular events with an achieved diastolic BP of 82.6 mmHg, and lowest CV mortality with diastolic BP of 86.5 mmHg but could not dispel the J-curve hypothesis (higher CV mortality in both ends of diastolic BP range) (35).

Cigarette smoking—The value of nicotine replacement therapy through transdermal systems (number needed to treat 16), nasal spray (number needed to treat 8), or nicotine gum (number needed to treat 17) in the achievement of smoking cessation has been well documented (36). Bupropion plus nicotine patch demonstrated greater efficacy in smoking cessation at 12 months (35.5%) when compared with nicotine replacement therapy alone (16.4%) (37).

Other—Hormonal replacement in postmenopausal women has been suggested as a valid intervention to prevent coronary events. The preliminary recommendations were based predominantly on observational studies. The potential benefit was partially attributed to the beneficial effect of estrogens on serum lipids. However, to exemplify the complexity of factors that participate in the atherosclerotic process and its complications, estrogen plus progestin therapy showed no benefit in cardiovascular event reduction in post-menopausal women with established coronary disease, despite significant lipid improvement (38).

Chronic Heart Failure

The treatment of chronic heart failure due to left ventricular systolic dysfunction has undergone rapid changes during the past 2 years. Conventional therapy recommended for general use includes diuretics, angiotensin-converting enzyme (ACE) inhibitors, and digitalis. There have been no long-term studies of loop diuretic therapy in heart failure; thus, the effects of diuretics on morbidity and mortality are not known. Results from the DIG trial (39) indicate that the primary benefit of digoxin in heart failure is to alleviate symptoms and improve clinical status, and thereby decrease the risk of hospitalization for heart failure. The drug appears to have little or no effect on survival. ACE inhibitors have been shown to alleviate symptoms and improve the clinical status of patients with CHF and to decrease the risk of death and hospitalization (40). New medications showing decreased morbidity and mortality in patients with chronic heart failure include beta-adrenergic blockers and aldosterone-receptor blockers.

Beta-adrenergic receptor blockers—Benefits from carvedilol were mentioned in the last update of Frontiers in Internal Medicine. In the second Cardiac Insufficiency Bisoprolol Study (CIBIS II) (41), 2,647 patients with moderate to severe heart failure (predominantly NYHA class III) were randomized to placebo or bisoprolol (up to 10 mg/day), which was added to conventional therapy for up to 28 months. Treatment with bisoprolol was associated with reduction in mortality hospitalization for any reason.

In the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) (42), 3,991 patients with chronic heart failure in NYHA functional class II-IV, established with optimum standard therapy, were randomized to placebo or metoprolol CR/XL (sustained release, up to 200 mg/day) for 6–20 months. All-cause mortality was lower in the metoprolol CR/XL group than in the placebo group (145 [7.2%], per patient-year of follow-up vs. 217 deaths [11.0%]). There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group, and deaths from worsening heart failure. Metoprolol CR/XL once daily in addition to optimum therapy improved survival. In both the CIBIS-II and the MERIT-HF, the

results led the Data and Safety Monitoring Boards to recommend early termination of the studies. Beta-blockers have now been evaluated in nearly 10,000 patients with heart failure who participated in over 20 placebo-controlled clinical trials. This collective experience indicates that, like ACE inhibitors, long-term treatment with β -blockers can lessen the symptoms of heart failure and improve the clinical status of patients with chronic heart failure. In addition, as with ACE inhibitors, β -blockers can decrease the risk of death as well as the combined risk of death or hospitalization (43).

Aldosterone-receptor blockers—Aldosterone plays an important role in the pathophysiology of heart failure (44). Aldosterone promotes the retention of sodium, the loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance. In the Randomized Aldactone Evaluation Study (RALES) (45), 1,663 patients with severe heart failure (class IV NYHA) were randomized to placebo or spironolactone (up to 25 mg daily), which was added to conventional therapy for a mean follow-up period of 24 months. Treatment with spironolactone was associated with a 30% reduction in risk of death and a 35% decrease in hospitalization for heart failure. These results led the Data and Safety Monitoring Board to recommend early termination of the study. Gynecomastia or breast pain was reported in 10% of men treated with spironolactone, as compared with 1% of men in the placebo group. The incidence of hyperkalemia was minimal in both groups of patients.

Cardiac Pacemakers

Pacing mode selection—Retrospective studies have provided an attractive hypothesis that atrial-based pacing, by preserving atrioventricular synchrony, prevents heart failure and atrial fibrillation, reduces the incidence of stroke, and decreases mortality. The first prospective randomized trial of pacemaker mode selection comparing AAI and VVI pacing was reported in 1994 in 225 patients with sinus node dysfunction (46). After a mean follow-up of 3.3 years, AAI pacing was associated with less atrial fibrillation and thromboembolism than VVI pacing, whereas there was no statistically significant difference in mortality or heart failure between the two treatment groups. In 1997, after an extended follow-up to a mean of 5.5 years, the beneficial effect of atrial pacing found in the initial study was enhanced substantially over time. Patients assigned to the AAI group had significantly lower all-cause and cardiovascular mortality. Furthermore, both atrial fibrillation and chronic atrial fibrillation were significantly reduced in the AAI group, as were thromboembolic events and heart failure. Atrioventricular block occurred in four patients in the atrial group (0.6% annual risk) (47). Therefore, based on the first prospective trial, it seems that AAI pacing is superior to VVI pacing in sick sinus syndrome. In the Pacemaker Selection in the Elderly (PASE) study (48), 407 patients 65 years of age or older received a dual-chamber pacemaker that had been randomly programmed to either ventricular pacing or dual-chamber pacing. The primary endpoint was health-related quality of life. Quality of life improved significantly after pacemaker implantation, but there were no differences between the two pacing modes in either quality of life or other pre-specified clinical outcomes (including cardiovascular events or death). Patients with sinus-node dysfunction, but not those with atrioventricular block, had moderately better quality of life and cardiovascular functional status with dual-chamber pacing than with ventricular pacing. Trends of borderline statistical significance in clinical endpoints favoring dual-chamber pacing were observed in patients with sinus-node dysfunction but not in those with atrioventricular block.

There are now three major trials designed and developed to test the value of physiological pacing against standard ventricular demand pacing: the Canadian Trial of Physiological Pacing (CTOPP); the Mode Selection Trial (MOST), and the United Kingdom Pacing and Cardiovascular Events (UKPACE). The latter two trials are still enrolling patients. In the CTOPP (49), 2,568 patients were randomized to VVI pacing or DDD/AAI (physiologic

pacing). There were more perioperative complications in patients receiving a physiologic system (9 vs. 3.8%). The physiologic group also was more likely to experience an inadequate pacing threshold (1.3 vs. 0.3%), inadequate sensing (2.2 vs. 0.5%), and more perioperative lead dislodgments (4.2 vs. 1.4%). At a mean follow-up of 36 months, there was no significant difference in stroke, cardiovascular death, or hospitalization for congestive heart failure between the two groups. However, at 2 years of follow-up, curves showing the incidence of atrial fibrillation (AF) began to diverge, favoring the physiologic group. This benefit remained at 36 months. Finally, there was no difference in either group in patients able to complete a 6-min walk test at 6 months—heart rate and distance walked was also nearly identical. This study demands that we rethink the role of physiologic pacing compared to ventricular pacing alone. Because the only differences are in the development of AF between the two groups, there may be little evidence to support the use of physiologic pacing in many patients. The cost implications of this study are equally important. However, we need to await the results of the other two major trials (MOST, UKPACE) before making final conclusions.

Acute Coronary Syndromes

Presently, acute coronary syndromes (ACS) is the preferred term to encompass unstable angina (UA), non-Q wave MI, and acute ST-elevation MI. All represent a different state of the same pathophysiologic process: a ruptured atherosclerotic plaque with activation of the coagulation cascade, and adhesion, activation, and aggregation of platelets.

The most important advances in this field in the last few years are as follows: (a) new platelet inhibitors, such as glycoproteins (GP) IIb/IIIa platelet receptor inhibitors (e.g., abciximab, eptifibatide, and tirofiban), clopidogrel, and ticlopidine; (b) low molecular weight heparins (enoxaparin and dalteparin) and (c) new studies establishing the superiority of PTCA over thrombolysis during acute ST-elevation MI.

GP IIb/IIIa is the receptor on platelets that binds plasma-borne adhesive proteins, such as fibrinogen and von Willebrand factor, allowing platelet aggregation. This is considered the final pathway of platelet aggregation. Agents that block this pathway are known as GP IIb/IIIa receptor antagonists and are considered the most powerful inhibitor of platelet aggregation during acute thrombosis (50).

The proposed mechanism of action of clopidogrel and ticlopidine is inhibition of the binding of adenosine 5'-diphosphate to its platelet receptor. Also, ticlopidine may interfere with the von Willebrand factor, resulting in less binding of this factor to platelets. Both agents are taken orally, their action is concentration-dependent, and maximal inhibition occurs at 4–7 days. The use of ticlopidine has been associated with thrombotic thrombocytopenic purpura and reversible neutropenia, while the side effect profile of clopidogrel does not differ much from that of aspirin (51). Ticlopidine has been shown to reduce the re-stenosis rate when used combined with aspirin in patients after coronary stent placement (52–54). There are no randomized controlled trials testing the use of clopidogrel as an adjunctive therapy after coronary stent placement in humans. However, clopidogrel is slowly replacing the use of ticlopidine for this purpose. This is probably due to its more benign side effect profile, as well as being backed up by the results of the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) where this agent was found to be safe, and superior to aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death in patients with coronary artery disease (55).

The low molecular weight heparins are fragments of unfractionated heparin produced by chemical processes that result in polysaccharide chains with a mean molecular weight of 5,000. Unfractionated heparin is a mixture of polysaccharide chains with a molecular weight ranging from 3,000–30,000. The main difference between these agents is their relative effect against

factor Xa and thrombin. Low molecular weight heparins have a greater activity against factor Xa, while unfractionated heparin has equivalent activity against both. This change is responsible for a two to four times longer plasma half-life than unfractionated heparin and a dose-independent clearance. Consequently, low molecular weight heparins have a more predictable anticoagulant response than unfractionated heparin, making laboratory monitoring unnecessary, except in patients with renal insufficiency (56).

Unstable Angina/non-Q Wave MI

Abciximab—In the CAPTURE (c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina) trial, 1,265 patients with UA refractory to aspirin and heparin, and one or more angiographic lesions suitable for PTCA, were randomized to receive abciximab or placebo for 18–24 h before, and 1 h after the PTCA procedure. Patients were followed for 6 months. The abciximab-treated group showed a 29% reduction of primary endpoint (composite of death, MI, or urgent intervention within the first 30 days) compared to the placebo-treated group (11.3 vs. 15.9%; $p = 0.012$) (57).

Tirofiban—In the PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management) trial, 3,232 patients with UA receiving aspirin were randomized to receive either tirofiban or intravenous heparin for 48 h. The group treated with tirofiban experienced a borderline reduction in the composite endpoint (death, MI, or refractory ischemia) at 48 h (3.8% for tirofiban vs. 5.6% for heparin, $p = 0.15$). At 30 days tirofiban treatment decreased the mortality by 39% (2.3% for tirofiban vs. 3.6% for heparin) (58).

In the PRISM-PLUS (Patients Limited by Unstable Signs and Symptoms) trial, 1,915 patients with UA at high risk for subsequent events who were receiving aspirin were randomized to tirofiban plus heparin, tirofiban alone, or heparin alone. The treatment arm receiving only tirofiban was dropped because of an increased death rate. The composite endpoint was reduced by 32% at 7 days in the group treated with tirofiban and heparin compared to heparin alone (12.9 vs. 17.9%). This benefit was maintained at 30 days (23% risk reduction, $p = 0.029$) and at 6 months (19% risk reduction, $p = 0.024$) (59).

The RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) trial included 2,141 patients undergoing PTCA within 72 h of presentation with UA or acute MI, who were randomized to receive placebo or tirofiban (bolus and 36 h infusion). At 2 days post-procedure there was a significant relative reduction in the composite endpoint (death, MI, CABG, repeat target vessel angioplasty, or stent insertion for actual or threatened abrupt closure) of 38% in the tirofiban group compared to the placebo group (5.4 vs. 8.7%). This significant reduction was maintained at 7 days, with a relative reduction of 27% in the tirofiban group compared to the placebo group (7.6 vs. 10.4%). However, the relative reduction was no longer statistically significant at 30 days or 6 months (60).

Eptifibatide—In the PURSUIT (Platelet GP IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial, 10,948 patients with UA or non-Q wave MI were randomized to receive either placebo or eptifibatide along with heparin and aspirin. At 30 days there was a 1.5% absolute reduction in death and MI in the eptifibatide-treated group compared to the placebo-treated group (14.2 vs. 15.7%, $p = 0.04$) (61).

At the time of the preparation of this manuscript, no single clinical trial showed extended survival after 1 month of the coronary event, when measured as a single endpoint. Long-term follow-up analyses of the main trials are now underway.

Low Molecular Weight Heparins

Enoxaparin—In the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events) study, 3,171 patients with UA or non-Q wave MI were randomized to receive subcutaneous enoxaparin twice daily or intravenous unfractionated heparin for 2–8 days. All patients received aspirin. The composite endpoint of death, MI, or recurrent angina was significantly reduced in the group receiving enoxaparin compared to the group receiving heparin, at 14 days and 30 days (16.6 vs. 19.8%, and 19.8 vs. 23.3%, respectively). Also, at 30 days, the group receiving enoxaparin required significantly fewer revascularization procedures than the group treated with unfractionated heparin (27.0 vs. 32.2%, $p = 0.001$) (62).

In the TIMI 11B (Thrombolysis in MI) trial, 4,020 patients with UA or non-Q wave MI were randomized to receive intravenous unfractionated heparin or subcutaneous enoxaparin twice-daily for 3 days. The enoxaparin group was continued on subcutaneous enoxaparin at a reduced twice-daily dose, while the unfractionated heparin group received placebo subcutaneous injections, both for 30 days. All patients received aspirin. The primary endpoint was the occurrence through day 43 of the composite of death, nonfatal MI, or recurrent ischemia requiring urgent revascularization. At day 14, the enoxaparin-treated group experienced a relative risk reduction of 15% compared to the unfractionated heparin-treated group (14.2 vs. 16.7%, $p = 0.03$). Also, all individual elements of the composite endpoint were reduced by enoxaparin. This benefit was maintained through day 43 (63).

Dalteparin—The FRISC (Fragmin During Instability in Coronary Artery Disease) trial compared subcutaneous dalteparin with placebo in patients with UA or non-Q wave MI. The rate of death or recurrent MI in the first 6 days was lower in the group assigned to dalteparin than in the group assigned to placebo (1.8 vs. 4.8%, $p = 0.001$). The need for revascularization was also lower in the dalteparin group (64).

Acute ST Elevation MI

Abciximab—In the TIMI 14 (Thrombolysis in MI) trial, 888 patients with ST-elevation presenting within 12 h from the onset of symptoms were randomized to receive the following: (a) accelerated dose alteplase (control), or (b) abciximab (bolus and 12 h infusion), or a combination of reduced doses of (c) alteplase and abciximab or (d) streptokinase and abciximab. Standard weight-adjusted heparin was used in the patients receiving alteplase alone, while low-dose weight-adjusted heparin was used in the patients for whom abciximab was part of the regimen. All patients received aspirin. The rate of TIMI 3 flow at 90 min in the group treated with alteplase alone was 57%, in those treated with abciximab alone was 32%, in the streptokinase-abciximab group was 34–46% (higher rates with increasing doses), and 76% in the alteplase-abciximab group. TIMI 3 flow rates in the alteplase-abciximab group were significantly higher than in the alteplase alone group at 60 min (72 vs. 43%, $p = 0.0009$) and at 90 min (77 vs. 62%, $p = 0.02$). In a dose confirmation phase, patients were randomized to three different groups: (a) alteplase alone; (b) alteplase-abciximab with low-dose heparin, and (c) alteplase-abciximab with very low-dose heparin. The rates of major hemorrhage were 6% in patients receiving alteplase alone, 7% in patients receiving alteplase-abciximab and low-dose heparin, and 1% in those receiving alteplase-abciximab and very low-dose heparin. In this study abciximab improved reperfusion without increasing the risk of major bleeding (65).

The RAPPORT (Reopro in Acute MI and Primary PTCA Organization Randomized Trial) study included 483 patients with acute MI, who were randomized to receive abciximab (bolus and infusion) or placebo. All patients received aspirin and full-dose heparin. Stent implantation was discouraged. The primary endpoint was a composite of death, recurrent MI, or urgent

revascularization. At 30 days, it was significantly lower in the abciximab group than in the placebo group (5.8 vs. 11.2%, $p = 0.03$). However, at 6 months the difference was borderline significant (11.6 vs. 17.8%, $p = 0.05$), or no longer significant if elective revascularization is included in the endpoint. Also, the rate of bleeding was higher in the abciximab-treated group (66).

Other studies where GP IIb/IIIa antagonists are used as an adjunctive therapy in patients with acute MI are in progress. It is worthwhile mentioning two of these studies, the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial, and the SPEED (Strategies for Patency Enhancement in Emergency Department) trial. The CADILLAC trial will randomize almost 2,000 patients through a factorial fashion to stent vs. no stent, and abciximab vs. no abciximab. It also will test the safety of early hospital discharge (within 2–3 days). The SPEED trial is evaluating different doses of r-PA in combination with abciximab (67).

PTCA/Stents—Several studies have shown that PTCA is superior to thrombolysis for the treatment of acute MI (68–70). Primary stenting during acute MI is safe and is associated with better survival and lower restenosis rates when compared to PTCA (71). Therefore, PTCA and stenting should be the preferred strategy for revascularization during any acute ST-elevation MI.

The GP IIb/IIIa antagonist trials have confirmed their clinical efficacy and safety as potent antiplatelet drugs in the treatment of ACS whether or not revascularization procedures are used. Their efficacy seems to be due to a class effect, at least until head-to-head comparisons are made. It is unknown whether long-term use of these agents will further improve outcomes; for this purpose the development of oral agents will be the greatest challenge. A recently published paper (72) that included all available trials where GP IIb/IIIa antagonists were used in patients with ACS showed a definite reduction in the composite endpoint of death and MI, and in the composite endpoint of death, MI, and the need for revascularization procedures. However, mortality was not significantly reduced, although a trend toward reducing it was observed. In the recent guidelines (73) for treatment of acute MI these agents have been recommended as a Class IIa intervention for patients experiencing a non-Q-wave MI who have some high-risk features and/or refractory ischemia, provided they do not have a major contraindication due to a bleeding risk.

Low molecular weight heparins are superior to unfractionated heparin during UA and non Q-wave MI. They are now recommended as a class IIa intervention during non-Q-wave MI, the same as unfractionated heparin (24).

It seems that clopidogrel will continue to replace ticlopidine after coronary stent placement due to the chemical similarity between these drugs, and the lesser side effects of clopidogrel, even in the absence of adequate scientific studies.

Percutaneous revascularization is preferred over thrombolytic agents in patients with acute ST-elevation MI who are admitted to a hospital where a high-volume cardiac catheterization laboratory exists, supported by experienced personnel, and if performed in a timely fashion.

Hematology

Hypercoagulable States

The description of mutation in the genes coding for either factor V or factor II (prothrombin) improved our understanding of the hypercoagulable state. Until recently, the coagulation pathway abnormalities identified that increased risk for thrombus formation were mainly

antithrombin III, protein C, and protein S deficiency, which are hereditary defects, or the presence of antiphospholipid antibodies, which is an acquired condition. Underlying hereditary defects were found to account for <10% of patients with spontaneous venous thrombosis while antiphospholipid antibodies were found in 10% of patients under age 50 (74). Therefore, the likelihood of determining a predisposing condition leading to spontaneous thrombus formation was found in <20% of cases.

In 1993, patients with deep venous thromboembolism (VTE) were described as having resistance to activated protein C, where a single point mutation at nucleotide 1691 of the factor V gene was identified in which the arginyl residue was replaced with glutamine, being termed factor V Leiden (FV R506Q) (75). These individuals had a mutated factor V that was resistant to cleavage by protein C, leading to a prothrombotic state. In the following years FVR506Q mutation became recognized as the most common hereditary predisposition to thrombus formation with an incidence of 3–8% in the general population, 20% in unselected patients with first-episode VTE, 50% incidence in familial thrombosis or recurrent venous thromboembolism, and in 40–60% of persons with hereditary hypercoagulable state (76,77). The risk of VTE is increased 5- to 10-fold in individuals heterozygous for FV R506Q mutation and 50- to 100-fold in homozygous individuals (78).

Recently, a mutation in the factor II gene has been described involving a G-to-A transition at nucleotide position 20210, being associated with an increased risk of VTE and with elevated prothrombin levels (79). This mutation is present in 1–2% of the general population, in 6% of patients with single VTE, and in 18% of patients with family history of thrombosis, being next to factor V Leiden, the second most frequently inherited abnormality leading to thrombosis (4).

However, both factor V Leiden and the prothrombin gene mutation by themselves are considered to be a mild hypercoagulable disorder because many carriers do not develop thrombosis until an advanced age, and some never develop a thrombotic episode. Therefore, the major contribution of this mutation may be when it coexists with other prothrombotic states that can either be congenital (AT-III, PC, PS deficiency, fibrinolytic abnormality) or acquired (pregnancy, oral contraceptives, immobilization, trauma, APL antibodies, or surgery). Of note, hyperhomocysteinemia, which is also considered an independent risk factor for thrombus formation, can be either hereditary or acquired. Because these mutations are relatively common in the general population, their coexistence with other risk factors is not unusual; therefore, coexistences magnify the risks of thrombosis. The role of these mutations in arterial thrombosis remains unclear.

In conclusion, tests of proven value in the work-up of the hypercoagulable state include AT-III, protein C and protein S deficiencies, factor V Leiden and factor II G20210A gene mutations, and antiphospholipid antibodies and homocysteine levels.

Gastroenterology

Gastroesophageal Reflux Disease (GERD) and Barrett's Esophagus

H. pylori and GERD. Overall, the available evidence indicates that *H. pylori* infection, particularly by cagA+ strains, protects against the development of GERD, or at least against its complications (80,81). One theory is that infected GERD patients are likely to respond better to antisecretory therapy in terms of their initial therapeutic response and frequency of relapse (82). The protective effect probably is largely a result of diminished acid secretion in patients with corpus gastritis with or without the neutralizing effect of ammonia produced by the urease activity of *H. pylori*. Nevertheless, additional studies are needed to confirm or refute these concepts by prospectively studying the relationship of the development of GERD to the

distribution of gastritis and the effects on acid secretion before and after *H. pylori* eradication in patients with peptic ulcer, non-ulcer dyspepsia, and clinically silent *H. pylori* infection. Preliminary data suggest that all such populations may be at risk of developing GERD after *H. pylori* eradication, although the risk may vary among these groups.

The subsequent risk in asymptomatic *H. pylori*-positive patients and those with non-ulcer dyspepsia is especially important because the value of eradication is not established under such conditions (83). In fact, proof that eradication of *H. pylori* causes GERD, a chronic disease with substantial morbidity and management cost, should caution concerning increasing enthusiasm for undertaking eradication in asymptomatic people and those with non-ulcer dyspepsia. However, the benefits of eradication in patients with peptic ulcer and primary B-cell lymphomas clearly outweigh the possible risk of developing GERD. Meanwhile, it is prudent to reserve *H. pylori* eradication for well-established indications, or until reliable methods are available for separating virulent strains from those that might exist in a commensal or symbiotic relationship with their human host (84).

Barrett's esophagus—Fifty years ago, only 2–3% of esophageal cancers were adenocarcinomas, the rest were squamous cell adenocarcinomas. Now adenocarcinomas account for over 50% of esophageal cancers in many reports (85). Most cases of esophageal adenocarcinoma arise from a Barrett's esophagus.

The long-term treatment consensus in patients with Barrett's esophagus includes a combination of removal of acid exposure from metaplastic epithelium combined with regular endoscopic and biopsy surveillance for evidence of malignant change.

More recent discussion has been centered on the best approach for patients showing evidence of high-grade dysplasia on biopsy. Arguments against a hard and fast decision for resection include the observation that the majority of these patients fail to show progression to adenocarcinoma with follow-up to over 9 years and that distal esophagectomy has a low but definite mortality rate (86). Proponents of esophagectomy argue that up to one-third of such patients will be found to have occult malignancy in the resected specimen.

Overall, the most compelling argument for maintaining a definite surveillance program in patients with Barrett's esophagus is the dramatic improvement in survival from adenocarcinoma discovered through this approach (87). A recent publication with a follow-up of over 100 months of 152 patients with Barrett's esophagus having antireflux surgery indicates asymptomatic failure rate of approximately 60% with 15 patients developing evidence of dysplasia and four patients having adenocarcinoma 7 years following the surgery (88). Improvements in acid suppressive therapy with the advent of proton pump inhibitors (PPI) offer the opportunity for chronic effective control of esophageal acid exposure with no evidence of adverse side effects to date. Similar to surgical series, there is lack of definitive evidence of regression of the metaplastic epithelium in reports of 67 and 72 months of follow-up. The question of whether more complete acid control, and with what regimen, will result in histologic regression of metaplastic epithelium remains to be resolved (89).

Photodynamic therapy (PDT) has been used extensively in the management of esophageal cancer and Barrett's esophagus with high-grade dysplasia (90). The endpoints of PDT have been to decrease the stage of dysplasia (i.e., from high-grade dysplasia to low-grade dysplasia or to completely eliminate the Barrett's segment). However, clinical trials report a low response rate for Barrett's esophagus (0–43%) and better results (88–100%) for high-grade dysplasia. There is no evidence that the ablation of Barrett's esophageal mucosa actually reduces the risk of esophageal cancer. PDT can be performed with a porphyrin compound in patients who are

not surgical candidates, recognizing that at the current time complications exist and there is not a proven benefit.

Gastrointestinal Cancer

Esophageal cancer—In the treatment of esophageal cancer, surgical technique appears to have improved during the past 20 years with the resectability rate increasing to the range of 50% and the perioperative mortality decreasing to less than 15%. However, the 5-year survival rate remains approximately 20% with the 5-year survival rate for all the patients with esophageal cancer being <10% (91). When administered in doses of 5,500–6,500 cGy, primary radiation therapy is associated with a 5-year survival rate no different from that of radical surgery (6–10%) without the preoperative morbidity. Recent efforts have been directed at assessing the merits of chemotherapy with or without radiation therapy preoperatively. The majority of these multimodality treatment programs have been uncontrolled; data from such experiences suggest that preoperative chemoradiation therapy will lead to a pathologic complete response (i.e., no residual tumor at time of surgery) in 15–20% of patients. Preliminary results of a randomized national intergroup trial comparing preoperative chemotherapy (5-fluorouracil + cisplatin) to immediate surgery have shown no difference in the rates of recurrence of survival after 2 years.

The results of a randomized trial comparing preoperative chemoradiation therapy to immediate surgery are conflicting. Experience at the University of Michigan in a total of 100 epithelial cell carcinomas or adenocarcinomas has not yet shown a statistically significant difference in probability of recurrence or survival between the two treatment strategies.

Other investigators have examined the addition of chemotherapy to radiation therapy in patients in whom surgical resection is not planned. Data from a randomized trial including 120 patients with localized squamous cell or adenocarcinoma of the esophagus, with a minimum follow-up time of 5 years, have shown a statistically significant prolongation in survival when 5-fluorouracil and cisplatin chemotherapy is given concomitantly with radiation therapy in comparison to radiation therapy alone (91).

Colorectal cancer—The most effective chemotherapeutic agent in the management of patients with metastatic disease remains to be 5-fluorouracil (5-FU), associated with a response rate of about 20% when given in standard doses and appearing to prolong survival in responding patients. Controlled trials using 5-FU-containing drug combinations, while initially encouraging, have shown no improvement over 5-FU alone.

Various pharmacological strategies have been undertaken to biologically enhance the activity of 5-FU. The most promising of these focus on the use of 5-FU in combination with leucovorin (i.e., folinic acid). 5-FU has been compared to 5-FU/leucovorin in nine randomized trials involving previously untreated patients with advanced colorectal cancer. The dose schedules of both the 5-FU and the leucovorin have varied in these trials. A meta-analysis of these studies has shown that the response rate has been enhanced statistically (usually doubled) when leucovorin has been added to 5-FU, but that there is little effect on overall survival (92).

Regarding adjuvant therapy for colon cancer, 5-FU has been used postoperatively as an adjuvant agent in patients with both colon and rectal cancers. However, a meta-analysis of the available data failed to reveal any benefit for the use of adjuvant 5-FU.

A survival benefit has been shown for patients with stage C disease when levamisole, an antihelminthic compound, was added to 5-fluorouracil. The contribution of levamisole to these “positive” results remains uncertain. Because the 5-FU/levamisole combination was not compared directly to 5-FU alone, it is conceivable that the data may be explained by the

administration of 5-FU in a more intensive, compliant manner than was used 25 years ago when initial 5-FU adjuvant trials were conducted. This benefit has not been observed in patients with stage B2 disease, possibly because the prognosis for such individuals with surgery alone is so favorable that a modest adjuvant effect would be masked unless examined in an enormous study population.

Additional controlled randomized trials have shown a survival benefit for patients treated with fluorouracil and leucovorin. Again, this benefit was noted in patients with stage C but not stage B disease. Recent studies have compared adjuvant 5-FU/levamisole to adjuvant FU/leucovorin with or without levamisole. The preliminary results of these trials suggest that 6 months of 5-FU/leucovorin is equivalent to 12 months of 5-FU/levamisole. Different dose schedules of 5-FU/leucovorin are similar in adjuvant efficacy but differ in toxicity profiles. Levamisole does not add benefit to the adjuvant effect of 5-FU/leucovorin.

Available data appear to support the use of postoperative therapy in patients with stage C disease. Such therapy may include 6 months of 5-fluorouracil and leucovorin or 12 months of 5-fluorouracil and levamisole. Prospective data have not yet demonstrated any adjuvant benefit for patients with stage B disease. Whether this treatment would improve the prognosis of individuals with such ominous factors as aneuploidy, mutated chromosome 18q. (i.e., DCC gene), or perforation remains to be determined.

Treatment of Viral Hepatitis

Hepatitis B—Interferon alpha has had beneficial impact in the treatment of the long-term natural history of hepatitis B. Interferon alpha has demonstrated to achieve a sustained suppression of HBV replication (HbeAg and HBV DNA undetectable in 30–40% of patients) (93). Among patients who lose HbeAg during therapy, long-term observation and comparison to untreated controls has documented an improvement in clinical outcome (reduced fatality, prolonged survival, and prolonged survival without complications of liver disease). Controversies exist over the value of interferon therapy in patients who acquired their HBV infections at birth. Such patients tend to be immunologically intolerant of HBV and to have a minimal elevation of aminotransferase activity. Similarly, sustained losses of HBV replication are unlikely in patients with chronic hepatitis B who are infected with HBV pre-core mutants.

Several different types of interferon alpha (recombinant, leukocyte, natural, consensus) and beta are available or are being studied in clinical trials; however, the data do not support the superiority of one preparation over others. Thymosin, a thymic extract presumed to stimulate cytolytic T cell activity, showed early promise in small clinical trial, but its efficacy was not supported by the results of a large, multicenter randomized, placebo-controlled clinical trials. Although cellular and gene therapy have been proposed experimentally on a limited basis, a role for these approaches will be practical only if more conventional therapy with nucleoside analogs is disappointing. Two orally administered nucleoside analogs, famciclovir and lamivudine, which inhibit reverse transcriptase activity, have been found to inhibit HBV replication substantially with negligible side effects, but the majority of patients treated by brief periods experience a return of HBV replication after cessation of therapy (94). Prolonging therapy may increase the likelihood of a sustained response. Other agents that are currently studied include the nucleoside analogs lobucavir and BMS 200475 and the nucleoside analog adefovir dipivoxil. Among patients treated for prolonged periods with lamivudine, mutations in the YMDD motif of the polymerase gene have been observed, although the clinical impact of these mutations remains to be demonstrated. The occurrence of such mutations points to the almost inevitable requirement for combination therapy, a subject that will be addressed in clinical trials. Finally, new attention has been focused on the potential for antibody (anti-HBs) therapy by the success of hepatitis B immune globulin (HBIG) to prevent the recrudescence

of hepatitis B after liver transplantation. Whether this percutaneous approach is practical or successful when compared to oral nucleoside analogs remains to be proven in clinical trials.

Hepatitis C—Reports describing the results of controlled trials suggested that interferon alpha therapy was associated with a 50% biochemical response rate, a 50% relapse rate in responders, and a sustained response rate of 25% (95). Patients who do not respond to therapy within the first 3 months are unlikely to respond thereafter. Among the biochemical responders to interferon in whom HCV RNA becomes detectable again 1 year after therapy, the likelihood of biochemical relapse is at least 50% over the course of 4 years (96). Trials of longer duration, higher-dose interferon therapy have conflicting results, but a consensus is emerging. Based upon recent trials and a recent meta-analysis of published trials, 12 months of therapy is associated with a higher sustained response rate of approximately 20%, but discontinuous therapy is not less effective than continuous therapy. The beneficial impact of interferon on the frequency of hepatocellular carcinoma in cirrhotic patients with hepatitis C has not been confirmed by several groups of investigators.

Sustained response to interferon is more likely in patients who have such baseline variables as shorter duration disease and/or younger age, milder histologic features, lower levels of HCV RNA, HCV genotypes other than 1, and limited quasispecies diversity. However, the patients most likely to benefit from interferon are those with early disease, precisely the patients whose disease is less likely to progress in the future.

Ribavirin, an oral nucleoside analog, was suggested in preliminary trials to have antiviral activity in chronic hepatitis C (97). Two large multicenter trials have failed to demonstrate a benefit of ribavirin monotherapy. Reports suggest that ribavirin in combination with interferon may provide sustained responsiveness in interferon-naïve patients, relapsing patients, and interferon nonresponders. In 1996, complete crystal structure of the protease of HCV was elucidated (98), and expectations are high that molecules can be designed to interfere with active sites and/or that pharmaceutical libraries of potential agents can be screened for specific activity against HCV protease activity (99).

Infectious Diseases

Antibiotic Resistance

A large amount of information indicates that very resistant pathogenic microorganisms will continue to be a problem in infectious diseases for years to come. Ever since the advent of penicillin, once thought to be the end of the microbial world, organisms have found ways to evade our potent armamentarium. The latest examples are the increasing incidences of vancomycin-resistant enterococci and *Staphylococcus aureus*, *Salmonella enteritica*, and *Streptococcus pneumoniae*.

The use of antimicrobials in food animals (especially penicillin and tetracycline) for growth promoting and for treating infections has led to the emergence of strains of *Salmonella enteritica* serotype *typhimurium* DT 104 resistant to five classes of antibiotics. In a study conducted by Glynn et al. (100), information was gathered from several reporting systems and the prevalence of this pathogen was studied. They estimated that of the 40,000 isolates reported annually, 3,400 are *typhimurium*-resistant to the five drugs (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline). The prevalence appears to be higher in western states of the U.S.

Additionally, they estimate that, due to underreporting, the true incidence of cases is much higher in the population (68,000–340,000 cases per year). The good news is that the previously

mentioned strains are all susceptible to fluoroquinolones as opposed to the European cases, this thought to be due to the limited veterinary use of such medications.

Strains of *Staphylococcus aureus* with intermediate resistance to vancomycin were first identified in Japan in 1996. Since then three cases (up to the time of this review) have been reported in the U.S. (101). Smith et al. in New Jersey and Michigan described the two initial cases. Intermediate resistance to vancomycin was defined by a minimal inhibitory concentration of 8–16 mcg/mL. In that report the authors followed the progression of the infection in the index cases and investigated personnel who had come in contact with them for the presence of the isolate. Both patients were on dialysis for renal failure, had been previously infected with methicillin-resistant *Staphylococcus aureus*, and received prolonged therapy for it. The mechanism of resistance is not clear but appears to be related to cellular modification due to prolonged vancomycin use as evidenced by the thickened extracellular material found in the isolates. None of the contacts were found to carry the organisms on their hands or in their nares. The findings of this study confirm the importance of proper infection control measures in the transmission of such resistant bacteria, which appears for now the best way to control the infection. It is important for hospitals and health care personnel to comply with the guidelines published by the CDC (102) to reduce the spread of glycopeptide-resistant strains of bacteria.

Neutropenia and Fever

In a recently published study, Freifeld et al. (103) randomized low-risk febrile neutropenic patients to receive oral amoxicillin-clavulanate plus ciprofloxacin or intravenous ceftazidime. Low risk was defined as neutropenia expected to resolve within 10 days and the absence of the following: hemodynamic instability; abdominal pain; nausea and vomiting; diarrhea; neurologic or mental status changes, and intravascular catheter infections, catheter tunnel infections, or new pulmonary infiltrates. In all, 116 episodes were studied. They found that treatment was successful without the need for modification in 71% of the episodes in the oral group vs. 67% in the intravenous group. If patients developed infections or microbiological data pointed to specific organisms, the regimen was changed to the appropriate antimicrobial agent. The regimen needed to be modified in 13% of episodes in the oral group vs. 32% of episodes in the intravenous group. Oral therapy was less well tolerated than intravenous therapy. The authors concluded that oral antibiotics are as effective as intravenous preparations in low-risk neutropenic febrile patients. Nonetheless, evidence is not yet strong enough to treat these patients at home, which is the ultimate objective of such studies. Close monitoring in a hospital setting is essential and may make the difference if life-threatening complications arise. Further randomized studies are needed to study this issue.

Endocarditis Prophylaxis

Antibiotic prophylaxis for bacterial endocarditis in patients with valvular heart disease undergoing treatment for dental procedures is a well-accepted practice among clinicians. Its use, however, has never been proven effective in human studies due, in part, to the low incidence of the disease.

Strom et al. (104) conducted a population-based, case-control study of 273 patients with proven bacterial endocarditis and matched controls. They found no increase in the risk of bacterial endocarditis in patients with valvular abnormalities undergoing dental procedures.

A probable risk was observed in those undergoing dental extractions, but it was based on only six patients and could not be adjusted for confounding factors; hence, it was likely a product of chance.

The authors estimate that antibiotic prophylaxis, if at all effective, will only reduce the risk of endocarditis by two cases per 1,000,000. Although the American Heart Association is very cautious in changing their recommendations, modifications will certainly occur in the future (105,106).

HIV/AIDS

As in bacterial infections, the transmission of multidrug-resistant HIV is worrisome. Because the widespread use of protease inhibitors began only 2 years ago, patients resistant to these drugs are not frequently encountered. Hetch et al. (107) described a patient with multidrug-resistant HIV virus in San Francisco. The patient who initially presented with acute retroviral syndrome was infected through anal intercourse with a poorly compliant HIV-infected patient who was tried in multiple drug regimens. The epidemiologic link was made due to the similarity in the HIV-1 env sequences from the two patients. Per the authors, the implications of this case are more importantly epidemiologic. The fact that the index case and the source thought it was safe to have unprotected sex withdrawing prior to ejaculation made them conclude that a lot of work is necessary concerning the manner of educating the general public. Also, proper surveillance of resistant viruses to implement an appropriate public health response is currently advocated.

The use of potent antiretroviral therapy and the introduction of protease inhibitors have decreased the morbidity and mortality of HIV infection over the last several years. In a study by Palella et al. (108), data was gathered from 1,255 patients participating in the HIV outpatient study. These were patients with at least one CD4 count of $<100/\text{mm}^3$. Over a 3-year period (1994–1997) a decline in mortality rate was consistently observed throughout the 3 years—from 29.4 per 100 person-years in 1994 to 8.8 per 100 person-years in 1997. These coincided with an increased use of protease inhibitors from 2% in 1994 to 82% in 1997. Although the authors acknowledge that the patients in the study may not represent the general population, it is encouraging to observe such a significant difference. For the future the challenges will be dealing with the resistance of the virus to these drugs and the important side effects of such medications that in some cases preclude their use.

Nephrology

The progression of renal disease in diabetic and non-diabetic patients remains a major challenge in nephrology. Angiotensin-converting enzyme inhibition (ACE-I) in hypertensive and normotensive microalbuminuric patients was shown to ameliorate the progression of renal disease in type I diabetics. These trials were discussed in the previous issue of “Frontiers”. Although the use of ACE-I in type II diabetics with hypertension is a common practice, no large trials with long-term follow-up exist to prove similar benefits observed in type I.

Type II patients account for the vast majority of diabetics overall, and 50% of the diabetics with end stage renal disease (ESRD). Whether patients with type II diabetes will benefit from early ACE-I preventing further renal disease remains to be answered.

In terms of progression of non-diabetic renal disease, several trials reported benefits of ACE-I. These studies were heterogeneous in terms of sample size and duration of follow-up. On the horizon are the mediators of non-hemodynamic mechanisms of renal injury such as the advanced glycation end-products and its inhibition by aminoguanidine.

Acute tubular necrosis remains a matter of great concern. The benefit of modern methods of dialysis remains to be proven. No convincing reduction in mortality has been observed with the newer dialytic modalities such as continuous renal replacement therapy. Medical

intervention to avoid or delay initiation of dialytic treatment and its potential complications has been studied recently.

This update will focus on recent studies evaluating the benefits of ACE inhibition in type II diabetics and non-diabetic patients with chronic progressive renal disease, and review the clinical use of anaritide, an ANP synthetic component in patients with acute tubular necrosis.

Type II Diabetes

It is well documented that the development of persistent microalbuminuria is a predictor of progression to end stage renal disease in diabetic patients. Monitoring the rate of albumin excretion is routinely used as a clinical indicator of future renal disease in this population. Whether the prevention of persistent microalbuminuria in type II diabetics without hypertension can be achieved was addressed by Ravid et al. (109). In a double-blind, placebo-controlled trial with a 6-year follow-up, a total of 156 normotensive, non-albuminuric patients were assigned to receive enalapril 10 mg/day or placebo. The albumin excretion in the placebo group and in the enalapril group at the beginning were 10.8 ± 8.0 mg/24 h and 11.6 ± 7.0 , respectively. After 6 years, the rate of excretion was 26.5 ± 10 mg/24 h, and 15.8 mg/24 h, which achieved statistically significant difference ($p < 0.001$). The transition to persistent microalbuminuric state occurred in 15 of 79 placebo patients against 5 of 77 enalapril-treated patients ($p = 0.042$), representing a risk reduction of 12.5% for development of microalbuminuria. In terms of renal function, the mean annual decrease in the placebo group was 0.04 mL/s while in the enalapril group it was 0.017 mL/s. At year 6, the creatinine clearance revealed a higher rate of decrease in renal function in the placebo group.

Of interest, although all patients maintained normal blood pressure throughout the study, the mean values for the enalapril group were lower than in the placebo group, which was statistically different at year 5.

Although it is very suggestive that ACE inhibition can attenuate the decline in renal function and delay the development of persistent microalbuminuria in this group of patients, the reduction in blood pressure itself could be a contribution to the reno-protective effect. Also, whether this initial benefit will represent further delay in the development of the overt nephropathy remains to be proven. Studies comparing ACE inhibitors with other anti-hypertensive agents in this population are necessary.

Recent studies have found the non-hemodynamic-mediated renal injury in diabetes such as the production of AGEs to be a result of a non-enzymatic reaction between protein and sugar. The accumulation of these products causes structural damage on various kinds of cells including mesangial cells. Administration of AGEs to animals produces renal lesions comparable to those occurring in early diabetic nephropathy (110). Aminoguanidine, a nucleophilic hydrazine, has shown to be capable of blocking the formation of AGEs in experimental studies with beneficial results (111). Whether these benefits will translate into clinical practice remains to be shown by clinical trials.

Non-Diabetic Renal Disease

Both diabetic and non-diabetic renal disease share several mechanisms of progression of renal injury; therefore, the question would be whether ACE-I would benefit these patients.

Several trials comparing ACE inhibitors to placebo or other anti-hypertensive agents were published with controversial results. Sample size, methods of evaluating renal function, duration of the study, and degree of renal insufficiency may be responsible for the differences among the trials. Recently, Giatras et al. (112) published a meta-analysis of a large number of randomized studies. It is important to emphasize that the authors included unpublished trials

as well. This is a valuable feature of this study, considering that a potential bias seen in meta-analytic studies due to the inclusion of published data only is avoided or at least decreased in this analysis.

A total of 1,594 patients were enrolled in 10 randomized studies (7 published and 3 unpublished), with at least 1-year follow-up. Endpoints such as relative risk for ESRD and for death differed among the trials. When the pooled relative risk for ESRD was calculated, the authors found a significantly lower risk (0.70) in the ACE-I group. In terms of relative risk for death the analysis showed no increase in risk.

It is important to emphasize that the benefits of the ACE-I could be attributed to greater reduction in blood pressure observed in the ACE group. Whether specific ACE inhibitor properties are responsible for the decrease in the risk of development of ESRD remains unclear.

Considering the results of the majority of the trials as well as the data discussed above, we recommend that ACE-I be considered first-line anti-hypertensive agents for patients with non-diabetic progressive renal disease.

Acute Tubular Necrosis (ATN)

It is well known that atrial natriuretic peptide (ANP) increases glomerular filtration rate by dilating afferent arterioles and constricting efferent arterioles. In experimental studies, infusion of ANP in animals with acute renal failure was shown to improve renal function.

A preliminary study in humans demonstrated that infusion of ANP improved renal function, thus decreasing the need for dialysis. A further multicenter, randomized, double-blind study was conducted by the Auriculin Anaritide Renal Failure Group and published recently (113). A total of 504 patients with ATN, both oliguric and non-oliguric, were enrolled in the study. Anaritide was infused for 24 h, one dose only. Endpoints were dialysis-free survival for 21 days after treatment, need for dialysis, changes in serum creatinine, and death. The authors concluded that administration of anaritide did not improve the overall rate of dialysis-free survival. A subgroup analysis comparing oliguric and non-oliguric patients revealed improved dialysis-free survival in oliguric patients and worsening in non-oliguric patients. Further trials are necessary to validate this intervention in patients with ATN.

The use of so-called renal dose dopamine has been a topic of great controversy. Although dopamine may cause an increase in GFR in patients with normal renal function, patients with a baseline GFR of <70 mL/min have not demonstrated an increase in GFR with low-dose dopamine infusion.

The use of fenoldopam mesylate, a benzazepine derivation of dopamine, is 10-fold more potent than dopamine at DA1 receptors and has about 1.6 times the maximal effect of dopamine at the level of both afferent and efferent arterioles. Again, clinical trials are needed to prove the clinical utility of this drug (114). Where an impact can still be made in the prevention of ATN involves fluid prophylaxis before contrast procedures and careful monitoring of nephrotoxic agents such as aminoglycosides (115).

Oncology

Prostate Cancer

Prostate cancer is the second most common cause of cancer deaths in the U.S., being the most common cancer detected in men. Even though in the past decade routine screening of asymptomatic men with prostate-specific antigen (PSA) became popular, large randomized trials supporting this approach are still lacking and its practice is not supported by any medical

organization at this time. Another area of uncertainty concerns the optimal management of men diagnosed with localized prostate cancer—aggressive (surgery, radiation) vs. conservative therapy (hormone, observation). The recent better understanding of the natural history of this disease is helping to answer this question.

The retrospective analysis by Albertsen et al. assessed the natural history of localized prostate cancer based on a competing risk analysis stratified by age at diagnosis and histology type in men managed conservatively with no treatment or hormonal therapy (116). A total of 767 men between the ages of 55 and 74 years were diagnosed with localized prostate cancer from 1971 and 1984. After a follow-up period of 15 years, men with well-differentiated tumor (Gleason score 2–4) had a minimal risk of death from prostate cancer (4–7%), while men with poorly differentiated tumors (Gleason score 7–10) faced a high risk of death from prostate cancer (42–87%). Men with moderately differentiated histology (Gleason score 5–6) had a modest risk of death from prostate cancer (6–30%). Therefore, for men with a 15-year life expectancy diagnosed with high-grade localized prostate cancer, it appears that conservative management is a poor choice. However, for those with low-grade tumor conservative management appears acceptable. The best approach for men with moderate-grade tumors remains unclear and further randomized clinical trials are important in order to answer this question.

Despite the controversy regarding the issues previously mentioned, it is generally accepted that patients with locally advanced disease do not do well with any therapy. For decades, androgen-deprivation therapy with gonadotropin-releasing hormone (GRH) agonists has been used to improve symptoms and to delay disease progression, with no impact on overall survival. In a randomized prospective trial, 415 patients with locally advanced prostate cancer were assigned to receive radiotherapy alone or radiotherapy plus immediate goserelin (GRH agonist) (117). After a median follow-up of 45 months, overall survival was 62% in the radiotherapy group vs. 79% in the combined treatment group ($p = 0.001$), with disease-free survival at 5 years of 48 and 85%, respectively ($p < 0.001$). In contrast to similar trials, this study showed the survival benefit of adjuvant goserelin when initiated at the beginning of external irradiation. Therefore, its use should be considered in patients with locally advanced prostate cancer.

Breast Cancer

Breast cancer remains the most common cancer in women, with an estimated 180,000 cases yearly resulting in 43,500 deaths. Due to the high cure rate with early detection, massive screening (secondary prophylaxis) with yearly mammography for women over the age 40 has been widely accepted and implemented. However, the role of primary prophylaxis remained unclear until recently. In the Breast Cancer Prevention Trial (BCPT P-1), 13,175 women who were considered to be at high risk for breast cancer were randomized to tamoxifen 20 mg/day or placebo for 5 years (118). High risk was defined as women with family history of breast cancer, nulliparity, history of atypical hyperplasia or lobular carcinoma, early menarche, or age >60 .

After a median follow-up of 3.6 years the study was terminated early when an interim analysis showed that the benefit of tamoxifen was already statistically significant with a 49% reduction in the incidence of invasive breast cancer ($p < 0.00001$). Among women with a prior history of lobular carcinoma, the reduced incidence was 56%. In October 1998 the FDA approved tamoxifen for preventing breast cancer for those women considered at high risk according to the selection criteria previously noted. Of note is that the risk assessment model used in this study did not include BRCA1 and BRCA2 genes because they were described at a later time. Therefore, new data analyses are being collected to determine the role of primary prophylaxis in women testing positive for these two genes.

A retrospective analysis done at the Mayo Clinic evaluated women at high risk for breast cancer based on family history who underwent bilateral prophylactic mastectomy (119). In an attempt to estimate the number of cases that would have been expected during the study period, the incidence of breast cancer among sisters who did not undergo surgery was evaluated. Of these sisters, diagnosis of breast cancer was made in 38.7%, in contrast to 1.4% (>90% reduction) among those who underwent prophylactic mastectomy. Because it is unlikely that a prospective randomized trial with a design similar to the Mayo Clinic study will be undertaken, this retrospective analysis most likely represents the best data in determining the impact of primary prophylaxis in the incidence of breast cancer.

Based on the results of these studies, women at high risk for breast cancer due to family history or personal history should be considered for primary prophylaxis. Even though women testing positive for BRCA genes 1 and 2 are at increased risk for breast cancer, there are no data currently available to support giving tamoxifen prophylactically to this population.

In contrast to the BCPT P-1 trial, two European trials failed to demonstrate the benefits of chemoprevention with tamoxifen in women at high risk for breast cancer (120,121). However, the number of women in these two trials was smaller and the population studied differed from the U.S. trial, having included women with hysterectomy and/or oophorectomy as well as including only specific high-risk groups such as women with a family history of breast cancer.

Pulmonary Medicine and Critical Care

Asthma

The past several decades have seen an evolution regarding the way we look at asthma. In the past, the most important elements in the pathogenesis of asthma were thought to be bronchial hyperresponsiveness leading to reversible airway obstruction. We now know that asthma is a chronic inflammatory disorder of the airways in which many cells, in particular mast cells, eosinophils, and T lymphocytes, are involved. This inflammation is associated with increased airway hyperresponsiveness. Currently the molecular mechanisms responsible for the different pathways involved in the inflammatory response are better understood. It is now recognized that the asthmatic response occurs as an immediate (acute) phase reaction, which is characterized by bronchoconstriction that develops within 15 min after antigen exposure and usually resolves within 1–2 h. In 30–70% of patients, a subsequent period of bronchoconstriction, the late asthmatic response, is seen. This phase typically begins 3–4 h after the primary insult and lasts up to 24 h. The late asthmatic response is associated with an increase in airway inflammatory cells as well as increased airway hyperresponsiveness that can persist for weeks (122). The acute phase reaction is the result of mast cell degranulation with mediator release after activation by antigen and cell-bound IgE. The major mediators involved are histamine and leukotrienes. The leukotrienes, in addition to causing bronchoconstriction, are also involved in the recruitment of inflammatory cells into the airways (123), thereby contributing to the late phase response. As a result of this new insight into the mechanisms that underlie asthma, the primary goal of any treatment aimed at asthma is the attenuation of airway inflammation. The new guidelines for the classification and management of asthma emphasize this point (124). Oral glucocorticoids have proven efficacy in acute asthmatic exacerbations and selected patients with severe asthma, but should be used as a last resort for continued use in patients with chronic asthma because of several well-known serious side effects. The mainstay of any intervention program targeted at patients with chronic asthma should be inhaled glucocorticoids. Regardless of the preparation used, even at high doses, side effects are relatively minor. A relatively new and reportedly more potent inhaled corticosteroid, fluticasone propionate, was studied in steroid-dependant asthmatics to evaluate its ability to reduce or possibly eliminate the need for oral steroids (125). Ninety-six patients with steroid-dependant asthma were randomized to receive either high-dose inhaled fluticasone propionate

(750 or 1,000 mcg bid) or placebo. At the end of 4 months, a total of 69% of patients in the fluticasone 750 mcg bid and 88% of patients in the 1,000 mcg bid treatment arms were able to discontinue prednisone. In the placebo arm, only 3% of patients were prednisone-free at 4 months. Patient-rated asthma symptoms as well as pulmonary function measured by spirometry also improved significantly in the treatment groups when compared to placebo. To date, there are no reports suggesting that long-term treatment with inhaled glucocorticoids is associated with an increased risk of fractures. The data on suppression of hypothalamic-pituitary-adrenal axis are somewhat more controversial. There are data to show that high doses of inhaled corticosteroids cause a dose-related decrease in a.m. cortisol and 24-h urine cortisol excretion, but the values remained in the normal range (126). Although it is unclear whether these findings actually transform into clinically relevant adrenal suppression, it appears that at the recommended doses, the inhaled corticosteroids are not associated with a significant suppression of the HPA axis.

The overall rate of systemic side effects can be significantly reduced with the use of a large volume spacer device. The leukotriene modifiers are a relatively new class of medications recently approved for the treatment of asthma. Currently there are two available preparations in the U.S., montelukast and zafirlukast. In a study of 146 patients with mild to moderate asthma, zafirlukast 20 mg bid administered with as needed β -2 agonists significantly reduced that use of rescue β -2 agonists, as well as days without asthma symptoms and number of days without episodes of asthma (127). Another study of 681 patients with mild to moderate asthma showed that montelukast 10 mg, qd when added to prn β -2 agonist use, significantly decreased asthma symptoms and prn β -2 agonist use as compared with placebo (128). It also improved pulmonary function as shown by increased forced expiratory volume in 1 sec (FEV-1) and morning as well as evening peak expiratory flow rate (PEFR). Both the treatment group and the placebo group had a similar percentage of patients on inhaled corticosteroids. Of interest is that the response to montelukast was not influenced by whether the patient was taking inhaled corticosteroids or not. This suggests that adding a leukotriene modifier to a background of inhaled corticosteroids has an additive effect. This should not come as a major surprise, because it has already been shown that corticosteroids do not inhibit the production of leukotrienes in the airways of patients with asthma. Montelukast has also been shown to provide significant protection against exercise-induced bronchoconstriction when compared to placebo (129). The question of which is more effective for the control of chronic asthma—inhaled corticosteroids or oral leukotriene modifiers—was answered at least partially by a recent study that compared oral montelukast 10 mg po qd, inhaled beclomethasone 200 mcg daily, and placebo in 895 patients with mild to moderate asthma. Both treatment groups had significantly improved FEV-1 and daytime symptoms as well as a decreased number of asthma exacerbations when compared to placebo (130). However, the overall clinical benefit was significantly greater with inhaled beclomethasone than with montelukast. Both medications had a similar side effect profile. In patients who are still symptomatic on high-dose inhaled corticosteroids, a possible option to increasing the dose of the inhaled steroids is adding a leukotriene modifier. Another option is to add a long-acting bronchodilator. In a study of 738 patients not well controlled on high doses of inhaled beclomethasone (500 mcg twice a day), the addition of a long-acting inhaled β -2 agonist (in two different doses of 50 mcg bid and 100 mcg bid) was compared to doubling the dose of the inhaled corticosteroid. The groups that were treated with the long-acting β -2 agonist significantly improved a.m. and p.m. PEFR as well as more symptom-free and rescue-medication-free days and nights (131). No difference was observed between the groups treated with the different doses of long-acting β -2 agonist. The most current guidelines in the management of asthma emphasize a stepwise approach to treatment in order to maximize the efficacy and decrease the side effects of multiple medications. The clinician must be the ultimate judge of the success of a particular intervention and decide when step-up therapy is warranted.

COPD

Chronic obstructive pulmonary disease (COPD) represents the fourth leading cause of death in the U.S. It is well established that smoking accounts for the great majority of cases, with α -1 antitrypsin deficiency, occupational exposures, and chronic infections accounting for the rest. It is well established that the only pharmacologic intervention shown to decrease mortality in COPD is the administration of oxygen, and although no other pharmacologic therapy has been shown to do this, some new therapies have been shown to be effective in the management of COPD. For patients with stable COPD, the combination of inhaled ipratropium and albuterol was shown to be more effective than either agent alone in improving pulmonary function (132). The use of the long-acting inhaled β -2 agonist salmeterol was shown to improve respiratory symptoms and to decrease the use of rescue β -2 agonists in patients with moderate to severe COPD when compared to placebo (133). Recently a placebo-controlled trial in patients with stable COPD showed that inhaled fluticasone improved spirometry and symptom scores. Although it did not decrease the number of exacerbations, it did decrease the severity of exacerbations (134). Fluticasone was well tolerated with no reported effect on mean serum cortisol concentration.

Guidelines for step-up therapy of stable COPD have been published elsewhere (135). For acute COPD exacerbations it has been shown that the use of inhaled ipratropium causes a significant increase in PaO_2 within 30 min after administration. In an acute exacerbation of COPD, the immediate goal is to improve airflow. For this purpose β -2 agonists are used. Their onset of action is faster than ipratropium. In clinical practice both agents are given simultaneously for acute exacerbations and although there is no solid evidence that the combination of these agents provides any benefit acutely, it has been suggested that the agents may act synergistically, but this is unclear. In patients with stable COPD only 20–30% show a clinically significant response to oral steroids. However, in patients with acute exacerbations and increased airway inflammation, a response to systemic steroids has been demonstrated. Erbland and colleagues (136) showed that in patients hospitalized with COPD exacerbations withholding systemic corticosteroids was associated with an increased number of treatment failures, worsening spirometry, and prolonged hospital stay. Another trial conducted in 27 outpatients with COPD exacerbation showed that the use of oral corticosteroids improved oxygenation, spirometry, and decreased the number of treatment failures (137). It has been shown that the most common identifiable cause of COPD exacerbations is an upper respiratory tract infection and in two-thirds of all exacerbations a potential bacterial pathogen has been identified. A recent meta-analysis of nine randomized, placebo-controlled trials of patients with COPD exacerbation showed a small, but statistically significant improvement in PEF in the antibiotic treatment group (138). The average change in peak flow rate was 10.75 L/min. Although this is a modest overall improvement, in patients with severe airflow limitation this change may be clinically important.

Despite appropriate medical therapy, patients with COPD continue to have a progressive decline in FEV-1. In patients with significant symptoms who are already on maximal medical therapy, a trial of pulmonary rehabilitation has been advocated. Recent data emerged clarifying this issue, at least in part. A randomized trial of 89 patients with severe COPD (FEV-1 <40%) in which patients received comprehensive pulmonary rehabilitation including exercise training, psychosocial support, and home training education showed that patients in the treatment group had improved exercise tolerance as well as improved health-related quality of life (139). Wedzicha and colleagues conducted a trial of pulmonary rehabilitation in 126 patients with severe COPD who were stratified by using the Medical Research Council (MRC) dyspnea scale as moderately or severely dyspneic. The moderately dyspneic patients had a significant improvement in exercise tolerance and quality of life compared to placebo (140). Interestingly, patients who were severely dyspneic did not show a significant improvement. These findings

suggest that pulmonary rehabilitation may be of benefit even in patients who do not have severe symptoms of COPD. For patients in whom medical therapy and an appropriately timed trial of pulmonary rehabilitation fail to achieve acceptable results in patient quality of life, lung volume reduction surgery should be considered. Even though the ideal candidates are not yet clearly defined, there are data that in selected patients the procedure results in improved pulmonary function and quality of life (141). Cooper et al. evaluated the procedure in 150 patients with severe emphysema ($FEV_1 < 25\%$). On the average, 20–30% of the volume of each lung was excised. The 90-day mortality was 4%. Results at 6 months of follow-up showed a 51% increase in FEV_1 . The average increase in PaO_2 was 8%. Re-evaluation at 1 and 2 years after surgery showed the benefit to be well maintained. Overall survival at 2 years post surgery was 92%. For a select group of patients lung volume reduction surgery is of proven benefit and a viable alternative to lung transplantation. There are currently no trials directly comparing mortality in patients with COPD treated with lung volume reduction surgery vs. conventional therapy. A large multicenter trial is currently underway to answer this question.

Pulmonary Embolism

Over the past few years, diagnosis and management of pulmonary embolism and deep venous thrombosis have changed significantly. Diagnosis of pulmonary embolism has always been difficult because the clinical findings usually are not specific and sometimes the findings on V/Q lung scan are not helpful. The main component in thrombi is fibrin; activation of the fibrinolytic system results in dissolution of cross-linked fibrin leading to formation of degradation products including D-dimer. In a trial of 1,177 patients with suspected pulmonary embolism, the D-dimer assay was shown to be useful in ruling out pulmonary embolism in patients with a nondiagnostic lung scan and a low pretest probability (142). Overall sensitivity and specificity of the D-dimer assay were 84.8 and 68.4, respectively. In patients with high pretest probability for pulmonary embolism, the sensitivity of the assay was 93% in ruling out pulmonary embolism. Therefore, in patients with high pretest probability for pulmonary embolism, even in the face of a negative D-dimer assay and a low probability lung scan, further studies are warranted. In patients with deep venous thrombosis, the recent approval of low molecular weight heparin administered subcutaneously has simplified management. In a randomized study of 500 patients (143), enoxaparin administered at home subcutaneously at a dose of 1 mg/kg twice a day was shown to be as effective as standard dose heparin administered intravenously in the hospital. In this study the rate of recurrent thrombosis and major bleeding were low in both groups and not statistically significant. All patients in this study additionally received oral anticoagulation with warfarin for the duration of the study, which was 90 days. Because deep venous thrombosis and pulmonary embolism are different expressions of the same disease, it would be expected that in patients with pulmonary embolism and no hemodynamic compromise, low molecular weight heparin could be a reasonable alternative to standard dose heparin. This issue was addressed by the THESEE investigators in a randomized trial of 612 patients with symptomatic pulmonary embolism who did not require thrombolytic therapy or embolectomy (144). Patients were given either full-dose unfractionated heparin intravenously or low molecular weight heparin (tinzaparin) subcutaneously. All patients received warfarin for the duration of the study. At the end of 3 months, there was no statistically significant difference between the study groups in the major endpoints, which were recurrent thromboembolism, major bleeding, and death. Although in the U.S. the standard of care is to admit patients with acute pulmonary embolism, this study suggests that in carefully selected patients treatment with low molecular weight heparin may be reasonable and cost-effective. Additional data from larger studies will be needed before this practice is accepted in the U.S., but the initial data are clearly promising.

Adult Respiratory Distress Syndrome (ARDS)

In spite of an ever expanding knowledge of the pathophysiology of cellular pathways and biochemical events that occur in ARDS, the syndrome remains associated with a mortality greater than 50% in affected patients (145). Early ARDS is associated with a widespread inflammatory response. Attempts at blunting the early inflammatory response with pharmacologic interventions have not met with success (146). Recently, Meduri et al. (147) attempted to target the fibroproliferative phase of ARDS, which is characterized by collagen synthesis eventually leading to acellular fibrosis, with a prolonged course of methylprednisolone. They studied 24 patients, 16 of whom received methylprednisolone in an initial dose of 2 mg/kg per day, tapered over 32 days. Eight patients received placebo. At the end of the study the patients in the treatment arm had a significantly reduced ICU and hospital-associated mortality. Treatment with methylprednisolone was also associated with a significant improvement in lung function, successful extubation, oxygenation, and decreased multiorgan dysfunction by day 10 of the study. The rate of infection per day of treatment was similar in both groups. Because of the small number of patients studied, these findings should be confirmed in larger trials, but data suggest that corticosteroids may play a role in the management of selected patients with ARDS.

Other agents recently studied in patients with ARDS are the antioxidants N-acetylcysteine and procysteine. In 46 patients with ARDS requiring mechanical ventilation, administration of these antioxidants shortened the duration of acute lung injury but did not have a significant effect on mortality (148). In patients with adult respiratory distress syndrome, there has been great interest in whether one particular ventilation strategy is superior to another. It is generally accepted that in patients with ARDS, lung compliance is decreased, and, therefore, as inflation pressures increase, risk of lung injury from alveolar overdistention increases. Based on this principle, a lung-protective approach in ventilated patients with ARDS has been studied for its effect on mortality. In a study of 53 patients with ARDS (149), 24 patients were treated with conventional ventilation and 29 were ventilated with a lung-protective strategy that consisted of maintaining low inspiratory driving pressures with low tidal volumes and acceptance of increased PaCO₂ levels to limit alveolar overdistention (permissive hypercapnia) while at the same time using levels of positive end expiratory pressure (PEEP) high enough to prevent alveolar collapse. After 28 days, 71% of patients in the conventional ventilation group died, compared with 38% in the protective ventilation group. The patients in the protective ventilation group also had improved weaning rates and lower rates of clinical barotrauma. However, the difference in survival to hospital discharge was not significant. The two ventilatory variables most strongly associated with treatment effect on mortality at 28 days were the use of high PEEP levels (preferentially above the lower inflection point on the pressure volume curve) and lower driving pressures (plateau pressure-PEEP). In patients with ARDS, the benefit of using high levels of PEEP seems to outweigh the negative effects of high distending pressures. This benefit is due at least in part to avoidance of hypoxemia and atelectasis.

Rheumatology

Advances in the field of rheumatology during the past 5 years were primarily focused on new treatments for rheumatoid arthritis (RA). These treatments include the use of biologic agents, new disease-modifying agents for the rheumatic diseases (DMARDs), or combinations of known DMARDs, and the use of metalloproteinases (minocycline).

Biologic Agents for the Treatment of Rheumatoid Arthritis

Production of tumor necrosis factor- α (TNF- α) by synovial macrophages plays an important role in disease activity in RA. In a multicenter study (150), 73 patients were randomly assigned

to single infusions of placebo vs. low (1 mg/kg) or high (10 mg/kg) doses of a monoclonal antibody (mAb) to TNF- α (cA2). At 4 weeks, intention-to-treat data analysis showed that 79 and 44% of patients treated with high dose and low dose of cA2, respectively, had 20% Paulus criteria for response to treatment. Placebo response was 8%. The mAb was well tolerated.

The long-term efficacy of anti-TNF- α therapy, as well as its effect on disease resistant to DMARDs, was determined in 101 patients with methotrexate (MTX)-resistant RA. Patients received intravenous cA2, with or without weekly MTX, at weeks 0, 2, 6, 10, and 14 of treatment (151) and were followed for 26 weeks. Sixty to seventy percent of patients receiving 1, 3, or 10 mg/kg cA2 with MTX therapy and 3 or 10 mg/kg cA2 without MTX achieved the 20% Paulus response. The study suggested that low-dose weekly MTX enhances the magnitude and duration of the action of cA2.

Other investigators have studied the effects of a soluble TNF- α receptor (p-75)-Fc fusion protein (etanercept). The safety, pharmacokinetics, and potential clinical efficacy of etanercept were evaluated in a multicenter, double-blind, placebo-controlled study in RA (152). One hundred eighty patients received 0.25, 2 or 16 mg/m² of subcutaneous etanercept or placebo, twice weekly, for 3 months. A 20% clinical response was observed in 75% of patients receiving the highest dose of etanercept vs. 14% with placebo ($p < 0.001$).

Another study addressed whether the addition of etanercept would provide additional benefit to patients with MTX-resistant RA (153). In a 24-week, double-blind trial, 89 patients were randomly assigned to receive subcutaneous etanercept (25 mg) or placebo, while continuing to receive MTX. At 24 weeks, 71% of patients receiving etanercept plus methotrexate and 27% of those receiving placebo plus MTX met the criteria for remission ($p < 0.001$). The only adverse events associated with etanercept were mild injection-site reactions.

Leflunomide

Leflunomide is a DMARD with immunosuppressive and anti-proliferative properties. In a phase II study (154), 402 patients with active RA were enrolled in a 6-month, multicenter, double-blind comparison of three dose levels of leflunomide (5, 10, or 25 mg) with placebo. Statistically significant improvement in primary and secondary outcome measures occurred in the 10- and 25-mg groups compared to placebo. Twenty-one patients (7%) in the active treatment groups withdrew due to adverse events, including transient elevation of liver function tests, abdominal pain, diarrhea, skin rash, reversible alopecia, and weight loss. A phase III study (155) of 358 RA patients compared leflunomide (100 mg daily on days 1–3, then 20 mg daily), placebo or sulfasalazine (0.5 g daily, titrated progressively to 2 g daily at week 4). The primary endpoints were tender and swollen joint counts and investigator and patient overall assessments. Leflunomide and sulfasalazine were significantly superior to placebo ($p = 0.0001$ for joint counts, $p < 0.001$ for assessments). Radiographic disease progression was significantly slower with leflunomide or sulfasalazine than with placebo, $p < 0.01$.

Combination DMARD Therapy

A multicenter trial (156) compared a step-down regimen of prednisolone (initially 60 mg/day, tapered to 7.5 mg/day, for 34 weeks), sulfasalazine (500 mg twice daily, then 2 g once daily), and MTX (7.7 mg weekly for 46 weeks), with sulfasalazine alone, in 155 patients in whom RA has been diagnosed in the last 2 years. Follow-up lasted 56 weeks. Patients had never been on DMARDs, except for antimalarials. After 28 weeks of treatment, a pooled outcome revealed that almost one-half of the patients receiving the combination therapy, but only one-fourth given monotherapy achieved 50% improvement according to ACR response criteria. Rates of remission were 28% for the combination group and 16% for the monotherapy group. After 12 months, differences between the two groups were not significant, but patients given

combination therapy had less erosive disease after 80 weeks of therapy. There were significantly fewer toxicity withdrawals seen in the combination group (8 vs. 29%, $p = 0.0008$), but more weight gain and early bone loss.

Another study (157) assessed the efficacy of combination of MTX and cyclosporine (CSA) in RA, in 148 patients followed for 6 months. Partial responders to 15 mg or less of MTX received (in addition to this medication) either CSA (2–2.5 mg/kg) or placebo. There were 19 withdrawals in the CSA group vs. 12 in the placebo group. Creatinine levels increased more in the CSA group ($p = 0.02$). A total of 48% of patients in the CSA group and 16% of the placebo patients met 20% ACR improvement criteria.

Another study (158) assessed the efficacy of a combination of MTX, sulfasalazine, and hydroxychloroquine, vs. MTX alone, vs. sulfasalazine and hydroxychloroquine, in 102 patients followed for 2 years. Triple therapy was as well tolerated as MTX alone. Withdrawals occurred for 19% of MTX patients, 9% of sulfasalazine-hydroxychloroquine patients and, 10% of patients in triple therapy. On the intention-to-treat analysis, 80% of the patients on triple therapy successfully completed the protocol (>50% improvement without significant side effects after 2 years). In contrast 40% of patients on sulfasalazine-hydroxychloroquine and 38% of patients on MTX alone completed the treatment.

Use of Minocycline in Early RA

In a multicenter trial (159), 46 patients with seropositive RA of <1 year duration, and who had not received systemic steroid therapy or DMARDs, were randomly assigned to receive 100 mg of minocycline orally or a matching placebo twice daily. Nonsteroidal anti-inflammatory agents (NSAIDs) were allowed. Sixty-five percent of minocycline recipients and 13% of controls experienced 50% or more improvement for 6 months or more. Minocycline continued to be advantageous when the study was unblinded for the final 6 months, and it reduced the need for DMARDs. Prevention of radiographic bone erosions was not measured.

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