from the director:

Tobacco use kills approximately 440,000 Americans each year, with one in every five U.S. deaths the result of smoking. Smoking harms nearly every organ in the body, causes many diseases, and compromises smokers’ health in general. Nicotine, a component of tobacco, is the primary reason that tobacco is addictive, although cigarette smoke contains many other dangerous chemicals, including tar, carbon monoxide, acetaldehyde, nitrosamines, and more.

An improved overall understanding of addiction and of nicotine as an addictive drug has been instrumental in developing medications and behavioral treatments for tobacco addiction. For example, the nicotine patch and gum, now readily available at drugstores and supermarkets nationwide, have proven effective for smoking cessation when combined with behavioral therapy.

Advanced neuroimaging technologies make it possible for researchers to observe changes in brain function that result from smoking tobacco. Researchers are now also identifying genes that predispose people to tobacco addiction and predict their response to smoking cessation treatments. These findings—and many other recent research accomplishments—present unique opportunities to discover, develop, and disseminate new treatments for tobacco addiction, as well as scientifically based prevention programs to help curtail the public health burden that tobacco use represents.

We hope this Research Report will help readers understand the harmful effects of tobacco use and identify best practices for the prevention and treatment of tobacco addiction.

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What Are the Extent and Impact of Tobacco Use?

According to the 2007 National Survey on Drug Use and Health, an estimated 70.9 million Americans aged 12 or older reported current use of tobacco—60.1 million (24.2 percent of the population) were current cigarette smokers, 13.3 million (5.4 percent) smoked cigars, 8.1 million (3.2 percent) used smokeless tobacco, and 2 million (0.8 percent) smoked pipes, confirming that tobacco is one of the most widely abused substances in the United States. Although the numbers of people who smoke are still unacceptably high, according

continued inside
to the Centers for Disease Control and Prevention there has been a decline of almost 50 percent since 1965.

NIDA’s 2008 Monitoring the Future survey of 8th-, 10th-, and 12th-graders, which is used to track drug use patterns and attitudes, has also shown a striking decrease in smoking trends among the Nation’s youth. The latest results indicate that about 7 percent of 8th-graders, 12 percent of 10th-graders, and 20 percent of 12th-graders had used cigarettes in the 30 days prior to the survey—the lowest levels in the history of the survey.

The declining prevalence of cigarette smoking among the general U.S. population, however, is not reflected in patients with mental illnesses. The rate of smoking in patients suffering from post-traumatic stress disorder, bipolar disorder, major depression, and other mental illness is two- to fourfold higher than in the general population; and among people with schizophrenia, smoking rates as high as 90 percent have been reported.

Tobacco use is the leading preventable cause of death in the United States. The impact of tobacco use in terms of morbidity and mortality to society is staggering. Economically, more than $96 billion of total U.S. health care costs each year are attributable directly to smoking.

However, this is well below the total cost to society because it does not include burn care from smoking-related fires, perinatal care for low-birthweight infants of mothers who smoke, and medical care costs associated with disease caused by secondhand smoke. In addition to health care costs, the costs of lost productivity due to smoking effects are estimated at $97 billion per year, bringing a conservative estimate of the economic burden of smoking to more than $193 billion per year.

How Does Tobacco Deliver Its Effects?

There are more than 4,000 chemicals found in the smoke of tobacco products. Of these, nicotine, first identified in the early 1800s, is the primary reinforcing component of tobacco.

Cigarette smoking is the most popular method of using tobacco; however, there has also been a recent increase in the use of smokeless tobacco products, such as snuff and chewing tobacco. These smokeless products also contain nicotine, as well as many toxic chemicals.

The cigarette is a very efficient and highly engineered drug delivery system. By inhaling tobacco smoke, the average smoker takes in 1–2 mg of nicotine per cigarette. When tobacco is smoked, nicotine rapidly reaches peak levels in the bloodstream and enters the brain. A typical smoker will take 10 puffs on a cigarette over a period of 5 minutes that
the cigarette is lit. Thus, a person who smokes about 1½ packs (30 cigarettes) daily gets 300 “hits” of nicotine to the brain each day. In those who typically do not inhale the smoke—such as cigar and pipe smokers and smokeless tobacco users—nicotine is absorbed through the mucosal membranes and reaches peak blood levels and the brain more slowly.

Immediately after exposure to nicotine, there is a “kick” caused in part by the drug’s stimulation of the adrenal glands and resulting discharge of epinephrine (adrenaline). The rush of adrenaline stimulates the body and causes an increase in blood pressure, respiration, and heart rate.

Is Nicotine Addictive?

Yes. Most smokers use tobacco regularly because they are addicted to nicotine. Addiction is characterized by compulsive drug seeking and abuse, even in the face of negative health consequences. It is well documented that most smokers identify tobacco use as harmful and express a desire to reduce or stop using it, and nearly 35 million want to quit each year. Unfortunately, more than 85 percent of those who try to quit on their own relapse, most within a week.

Research has shown how nicotine acts on the brain to produce a number of effects. Of primary importance to its addictive nature are findings that nicotine activates reward pathways—the brain circuitry that regulates feelings of pleasure. A key brain chemical involved in mediating the desire to consume drugs is the neurotransmitter dopamine, and research has shown that nicotine increases levels of dopamine in the reward circuits. This reaction is similar to that seen with other drugs of abuse and is thought to underlie the pleasurable sensations experienced by many smokers. For many tobacco users, long-term brain changes induced by continued nicotine exposure result in addiction.

Nicotine’s pharmacokinetic properties also enhance its abuse potential. Cigarette smoking produces a rapid distribution of nicotine to the brain, with drug levels peaking within 10 seconds of inhalation. However, the acute effects of nicotine dissipate quickly, as do the associated feelings of reward, which causes the smoker to continue dosing to maintain the drug’s pleasurable effects and prevent withdrawal.

Nicotine withdrawal symptoms include irritability, craving, depression, anxiety, cognitive and attention deficits, sleep disturbances, and increased appetite. These symptoms may begin within a few hours after the last cigarette, quickly driving people back to tobacco use. Symptoms peak within the first few days of smoking cessation and usually subside within a few weeks. For some people, however, symptoms may persist for months.

Although withdrawal is related to the pharmacological effects of nicotine, many behavioral factors can also affect the severity of withdrawal symptoms. For some people, the feel, smell, and sight of a cigarette and the ritual of obtaining, handling, lighting, and smoking the cigarette are all associated with the pleasurable effects of smoking and can make withdrawal or craving worse. Nicotine replacement therapies such as gum, patches, and inhalers may help alleviate the pharmacological aspects of withdrawal; however, cravings often persist. Behavioral therapies can help smokers identify environmental triggers of craving so they can employ strategies to prevent or circumvent these symptoms and urges.
Are There Other Chemicals That May Contribute to Tobacco Addiction?

Yes, research is showing that nicotine may not be the only ingredient in tobacco that affects its addictive potential. Using advanced neuroimaging technology, scientists can see the dramatic effect of cigarette smoking on the brain and are finding a marked decrease in the levels of monoamine oxidase (MAO), an important enzyme that is responsible for the breakdown of dopamine. This change is likely caused by some ingredient in tobacco smoke other than nicotine, because we know that nicotine itself does not dramatically alter MAO levels. The decrease in two forms of MAO (A and B) results in higher dopamine levels and may be another reason that smokers continue to smoke—to sustain the high dopamine levels that lead to the desire for repeated drug use.

Animal studies by NIDA-funded researchers have shown that acetaldehyde, another chemical found in tobacco smoke, dramatically increases the reinforcing properties of nicotine and may also contribute to tobacco addiction. The investigators further report that this effect is age-related: adolescent animals display far more sensitivity to this reinforcing effect, which suggests that the brains of adolescents may be more vulnerable to tobacco addiction.

What Are the Medical Consequences of Tobacco Use?

Cigarette smoking kills an estimated 440,000 U.S. citizens each year—more than alcohol, illegal drug use, homicide, suicide, car accidents, and AIDS combined. Between 1964 and 2004, more than 12 million Americans died prematurely from smoking, and another 25 million U.S. smokers alive today will most likely die of a smoking-related illness.

Cigarette smoking harms nearly every organ in the body. It has been conclusively linked to cataracts and pneumonia, and accounts for about one-third of all cancer deaths. The overall rates of death from cancer are twice as high among smokers as nonsmokers, with heavy smokers having rates that are four times greater than those of nonsmokers. Foremost among the cancers caused by tobacco use is lung cancer—cigarette smoking has been linked to about 90 percent of all cases of lung cancer, the number one cancer killer of both men and women. Smoking is also associated with cancers of the mouth, pharynx, larynx, esophagus, stomach, pancreas, cervix, kidney, bladder, and acute myeloid leukemia.

In addition to cancer, smoking causes lung diseases such as chronic bronchitis and emphysema, and it has been found to exacerbate asthma symptoms in adults and children. About 90 percent of all deaths from chronic obstructive pulmonary diseases are attributable to cigarette smoking. It has also been well documented that smoking substantially increases the risk of heart disease, including stroke, heart attack, vascular

Using advanced neuroimaging technology, scientists can see the dramatic effect of cigarette smoking on the brain and body and are finding a marked decrease in the levels of monoamine oxidase (MAO B), an important enzyme that is responsible for the breakdown of dopamine. (Source: Fowler et al., 2003)
disease, and aneurysm. Smoking causes coronary heart disease, the leading cause of death in the United States: cigarette smokers are 2–4 times more likely to develop coronary heart disease than nonsmokers.

Exposure to high doses of nicotine, such as those found in some insecticide sprays, can be extremely toxic as well, causing vomiting, tremors, convulsions, and death. In fact, one drop of pure nicotine can kill a person. Nicotine poisoning has been reported from accidental ingestion of insecticides by adults and ingestion of tobacco products by children and pets. Death usually results in a few minutes from respiratory failure caused by paralysis.

Although we often think of medical consequences that result from direct use of tobacco products, passive or secondary smoke also increases the risk for many diseases. Environmental tobacco smoke is a major source of indoor air contaminants; secondhand smoke is estimated to cause approximately 3,000 lung cancer deaths per year among nonsmokers and contributes to more than 35,000 deaths related to cardiovascular disease. Exposure to tobacco smoke in the home is also a risk factor for new cases and increased severity of childhood asthma. Additionally, dropped cigarettes are the leading cause of residential fire fatalities, leading to more than 1,000 deaths each year.

Are There Safe Tobacco Products?

The adverse health effects of tobacco use are well known, yet many people do not want to quit or have difficulty quitting. As a result, there has been a recent surge in the development of tobacco products that claim to reduce exposure to harmful tobacco constituents or to have fewer health risks than conventional products. These “potentially reduced exposure products” (PREPs), which include cigarettes and smokeless tobacco (e.g., snuff, tobacco lozenges), have not yet been evaluated sufficiently to determine whether they are indeed associated with reduced risk of disease. Recent studies indicate that the levels of carcinogens in these PREPs range from relatively low to comparable to conventional tobacco products. These studies conclude that medicinal nicotine (found in the nicotine patch and gum) is a safer alternative than these modified tobacco products.
Tobacco Use and Comorbidity

There is clear evidence of high rates of psychiatric comorbidity, including other substance abuse, among adolescents and adults who smoke. For example, it has been estimated that individuals with psychiatric disorders purchase approximately 44 percent of all cigarettes sold in the United States, which undoubtedly contributes to the disproportionate rates of morbidity and mortality in these populations. In addition, studies have shown that as many as 80 percent of alcoholics smoke regularly, and that a majority of them will die of smoking-related, rather than alcohol-related, disease.

In young smokers, the behavior appears to be strongly associated with increased risk for a variety of mental disorders. In some cases—such as with conduct disorders and attention-deficit hyperactivity disorder—these disorders may precede the onset of smoking, while in others—such as with substance abuse—the disorders may emerge later in life. Whether daily smoking among boys and girls is the result or the cause of a manifest psychiatric condition, it is troubling that so very few adolescents have their nicotine dependence diagnosed or properly treated. Preventing the early onset of smoking and treating its young victims are critical primary-care priorities, the fulfillment of which could have a dramatic impact on our ability to prevent or better address a wide range of mental disorders throughout life.

Among adults, the rate of major depressive episodes is highest in nicotine-dependent individuals, lower in nondependent current smokers, and lowest in those who quit or never started smoking. Furthermore, there is evidence showing that, for those who have had more than one episode, smoking cessation may increase the likelihood of a new major depressive episode. Adult tobacco use also increases risk for the later development of anxiety disorders, which may be associated with an increased severity of withdrawal symptoms during smoking cessation therapy. But the most extensive comorbidity overlap is likely the one that exists between smoking and schizophrenia, since, in clinical samples, the rate of smoking in patients with schizophrenia has ranged as high as 90 percent.

Smoking and Pregnancy—What Are the Risks?

In the United States, it is estimated that about 16 percent of pregnant women smoke during their pregnancies. Carbon monoxide and nicotine from tobacco smoke may interfere with the oxygen supply to the fetus. Nicotine also readily crosses the placenta, and concentrations in the fetus can be as much as 15 percent higher than maternal levels. Nicotine concentrates in fetal blood, amniotic fluid, and breast milk. Combined, these factors can have severe consequences for the fetuses and infants of smoking mothers. Smoking during pregnancy caused an estimated 910 infant deaths annually from 1997 through 2001, and neonatal care costs related to smoking are estimated to be more than $350 million per year.

The adverse effects of smoking during pregnancy can include fetal growth retardation and decreased birthweight. The decreased birthweights seen in infants of mothers who smoke reflect a dose-dependent relationship—the more the woman smokes during pregnancy, the greater the reduction of infant birthweight. These newborns also display signs of stress and drug withdrawal consistent with what has been reported in infants exposed to other drugs. In some cases, smoking during pregnancy may be associated with spontaneous abortions and sudden infant death syndrome (SIDS), as well as learning and behavioral problems and an increased risk of obesity in children. In addition, smoking more than one pack a day during pregnancy nearly doubles the risk that the affected child will become addicted to tobacco if that child starts smoking.
Smoking and Adolescence

In 2007, more than 3 million American adolescents (aged 12–17) reported using a tobacco product in the month prior to the survey. In that same year it was found that nearly 60 percent of new smokers were under the age of 18 when they first smoked a cigarette. Of smokers under 18, more than 6 million will likely die prematurely from a smoking-related disease.

Tobacco use in teens is not only the result of psychosocial influences, such as peer pressure; recent research suggests that there may be biological reasons for this period of increased vulnerability. There is some evidence that intermittent smoking can result in the development of tobacco addiction in some teens. Animal models of teen smoking provide additional evidence of an increased vulnerability. Adolescent rats are more susceptible to the reinforcing effects of nicotine than adult rats, and take more nicotine when it is available than do adult animals.

Adolescents may also be more sensitive to the reinforcing effects of nicotine in combination with other chemicals found in cigarettes, thus increasing susceptibility to tobacco addiction. As mentioned above, acetaldehyde increases nicotine’s addictive properties in adolescent, but not adult, animals. A recent study also suggests that specific genes may increase risk for addiction among people who begin smoking during adolescence. NIDA continues to actively support research aimed at increasing our understanding of why and how adolescents become addicted, and to develop prevention and treatment strategies to meet their specific needs.

Are There Gender Differences in Tobacco Smoking?

Several avenues of research now indicate that men and women differ in their smoking behaviors. For instance, women smoke fewer cigarettes per day, tend to use cigarettes with lower nicotine content, and do not inhale as deeply as men. However, it is unclear whether this is due to differences in sensitivity to nicotine or other factors that affect women differently, such as social factors or the sensory aspects of smoking.

The number of smokers in the United States declined in the 1970s and 1980s, remained relatively stable throughout the 1990s, and

Large-scale smoking cessation trials show that women are less likely to initiate quitting and may be more likely to relapse if they do quit.
declined further through the early 2000s. Because this decline in smoking was greater among men than women, the prevalence of smoking is only slightly higher for men today than it is for women. Several factors appear to be contributing to this narrowing gender gap, including women being less likely than men to quit. Large-scale smoking cessation trials show that women are less likely to initiate quitting and may be more likely to relapse if they do quit. In cessation programs using nicotine replacement methods, such as the patch or gum, the nicotine does not seem to reduce craving as effectively for women as for men. Other factors that may contribute to women’s difficulty with quitting are that withdrawal may be more intense for women or that women are more concerned about weight gain.

Although postcessation weight gain is typically modest (about 5–10 pounds), concerns about this may be an obstacle to treatment success. In fact, NIDA research has found that when women’s weight concerns were addressed during cognitive-behavioral therapy, they were more successful at quitting than women who were in a program designed only to attenuate postcessation weight gain. Other NIDA researchers have found that medications used for smoking cessation, such as bupropion and naltrexone, can also attenuate postcessation weight gain and could become an additional strategy for enhancing treatment success.

It is important for treatment professionals to be aware that standard regimens may have to be adjusted to compensate for gender differences in nicotine sensitivity and in other related factors that contribute to continued smoking.

Are There Effective Treatments for Tobacco Addiction?

Yes, extensive research has shown that treatments for tobacco addiction do work. Although some smokers can quit without help, many individuals need assistance with quitting. This is particularly important because smoking cessation can have immediate health benefits. For example, within 24 hours of quitting, blood pressure and chances of heart attack decrease.

Nicotine replacement therapies (NRTs), such as nicotine gum and the transdermal nicotine patch, were the first pharmacological treatments approved by the Food and Drug Administration (FDA) for use in smoking cessation therapy. NRTs are used (in conjunction with behavioral support) to relieve withdrawal symptoms—they produce less severe physiological alterations than tobacco-based systems and generally provide users with lower overall nicotine levels than they receive with tobacco. An added benefit is that these forms of nicotine have little abuse potential since they do not produce the pleasurable effects of tobacco products, nor do they contain the carcinogens and gases associated with tobacco smoke. Behavioral treatments, even beyond what is recommended on packaging labels, have been shown to enhance the effectiveness of NRTs and improve long-term outcomes.

The FDA’s approval of nicotine gum in 1984 marked the availability (by prescription) of the first NRT on the U.S. market. In 1996, the FDA approved Nicorette gum for over-the-counter (OTC) sales. Whereas nicotine gum provides some smokers with the desired control over dose and the ability to relieve cravings, others are unable to tolerate the taste and chewing demands. In 1991 and 1992, the FDA approved four transdermal nicotine replacement therapies.
nicotine patches, two of which became OTC products in 1996. In 1996 a nicotine nasal spray, and in 1998 a nicotine inhaler, also became available by prescription, thus meeting the needs of many additional tobacco users. All the NRT products—gum, patch, spray, and inhaler—appear to be equally effective.

Additional Medications
Although the primary focus of pharmacological treatments for tobacco addiction has been nicotine replacement, other treatments are also available. For example, the antidepressant bupropion was approved by the FDA in 1997 to help people quit smoking and is marketed as Zyban. Varenicline tartrate (Chantix) is a medication that recently received FDA approval for smoking cessation. This medication, which acts at the sites in the brain affected by nicotine, may help people quit by easing withdrawal symptoms and blocking the effects of nicotine if people resume smoking.

Several other nonnicotine medications are being investigated for the treatment of tobacco addiction, including other antidepressants and an antihypertensive medication. Scientists are also investigating the potential of a vaccine that targets nicotine for use in relapse prevention. The nicotine vaccine is designed to stimulate the production of antibodies that would block access of nicotine to the brain and prevent nicotine’s reinforcing effects.

Behavioral Treatments
Behavioral interventions play an integral role in smoking cessation treatment, either in conjunction with medication or alone. A variety of methods can assist smokers with quitting, ranging from self-help materials to individual cognitive-behavioral therapy. These interventions teach individuals to recognize high-risk smoking situations, develop alternative coping strategies, manage stress, improve problem-solving skills, and increase social support. Research has also shown that the more therapy is tailored to a person’s situation, the greater the chances are for success.

Traditionally, behavioral approaches were developed and delivered through formal settings, such as smoking cessation clinics and community and public health settings. Over the past decade, however, researchers have been adapting these approaches for mail, telephone, and Internet formats, which can be more acceptable and accessible to smokers who are trying to quit. In 2004, the U.S. Department of Health and Human Services (HHS) established a national toll-free number, 800-QUIT-NOW (800-784-8669), to serve as a single access point for smokers seeking information and assistance in quitting. Callers to the number are routed to their State’s smoking cessation quitline or, in States that have not established quitlines, to one maintained by the National Cancer Institute. In addition, a new HHS Web site (www.smokefree.gov) offers online advice and downloadable information to make cessation easier.

Quitting smoking can be difficult. People can be helped during the time an intervention is delivered; however, most intervention programs are short-term (1–3 months). Within 6 months, 75–80 percent of people who try to quit smoking relapse. Research has now shown that extending treatment beyond the typical duration of a smoking cessation program can produce quit rates as high as 50 percent at 1 year.
New Frontiers in Tobacco Research

If so many smokers want to quit, why are few able to do so successfully? To address this question, scientists are increasingly focusing on the powerful role of genetics in addiction. Twin studies indicate that approximately 40–70 percent of a person’s risk of becoming addicted to nicotine depends on his or her genes. Although complex diseases like addiction involve large numbers of genes interacting with a wide variety of environmental factors, the contribution of a particular gene can be substantial:

Genetic variants associated with nicotine metabolism, for example, have been shown to influence how people smoke such that slow metabolizers smoke fewer cigarettes per day and have a higher likelihood of quitting, and that there is greater abstinence among individuals receiving nicotine patch therapy. A recent NIDA-funded study identified a variant in the gene for a nicotinic receptor subunit that doubled the risk for nicotine addiction among smokers. A subsequent study found that this gene variant also increased susceptibility to the severe health consequences of smoking, including lung cancer and peripheral arterial disease. NIDA is currently supporting large-scale genome-wide association studies to uncover additional genetic risk factors in order to better understand tobacco addiction and its adverse effects on health.

In addition to predicting an individual’s risk for nicotine addiction, genetic markers can also help predict whether medications (like bupropion) will effectively help a smoker quit. This takes root in the emerging field of pharmacogenomics, which investigates how genes influence a patient’s response to drugs and medications. In the future, genetic screening could help clinicians select treatments, adjust dosages, and avoid or minimize adverse reactions, tailoring smoking cessation therapies to an individual’s unique genetic inheritance.

Glossary

Addiction: A chronic, relapsing disease characterized by compulsive drug seeking and abuse and by long-lasting neurochemical and molecular changes in the brain.

Adrenal glands: Glands located above each kidney that secrete hormones, e.g., adrenaline.

Craving: A powerful, often uncontrollable desire for drugs.

Dopamine: A neurotransmitter present in regions of the brain that regulate movement, emotion, motivation, and feelings of pleasure.

Emphysema: A lung disease in which tissue deterioration results in increased air retention and reduced exchange of gases. The result is difficulty breathing and shortness of breath.

Neurotransmitter: A chemical that acts as a messenger to carry signals or information from one nerve cell to another.

Nicotine: An alkaloid derived from the tobacco plant that is primarily responsible for smoking’s psychoactive and addictive effects.

Pharmacokinetics: The pattern of absorption, distribution, and excretion of a drug over time.

Tobacco: A plant widely cultivated for its leaves, which are used primarily for smoking; the N. tabacum species is the major source of tobacco products.

Withdrawal: A variety of symptoms that occur after chronic use of an addictive drug is reduced or stopped.
References


Where Can I Get More Scientific Information on Tobacco Addiction?

To learn more about tobacco and other drugs of abuse, or to order materials on these topics free of charge in English or Spanish, visit the NIDA Web site at www.drugabuse.gov or contact the DrugPubs Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

What’s New on the NIDA Web Site
- Information on drugs of abuse
- Publications and communications (including NIDA Notes and Addiction Science & Clinical Practice journal)
- Calendar of events
- Links to NIDA organizational units
- Funding information (including program announcements and deadlines)
- International activities
- Links to related Web sites (access to Web sites of many other organizations in the field)

NIDA Web Sites
- drugabuse.gov
- backtoschool.drugabuse.gov
- smoking.drugabuse.gov
- teens.drugabuse.gov

For Physician Information
- NIDAMED
  - www.drugabuse.gov/nidamed

Other Web Sites
Information on tobacco addiction is also available through these other Web sites:
- Centers for Disease Control and Prevention: www.cdc.gov/tobacco
- National Cancer Institute: www.cancer.gov
- U.S. Department of Health and Human Services: www.smokefree.gov
- Substance Abuse and Mental Health Services Administration Health Information Network: www.samhsa.gov/shin
- Society for Research on Nicotine and Tobacco: www.srnt.org
- NicNet: www.nicnet.org
- The Robert Wood Johnson Foundation: www.rwjf.org
- Join Together Online: www.quitnet.org
- American Legacy Foundation: www.americanlegacy.org