specialists. Most important, as Barrie points out, each patient requires an individualized approach to management, aiming therapy at those components of the disease that are most troublesome to that particular patient.

There is currently no effective means to prevent ophthalmopathy or to predict which patients with Graves' hyperthyroidism are most likely to go on to have substantial eye disease. Further, because of possible medical side effects and risks inherent in the surgical procedures available, treatment is reserved primarily for patients with advanced, severe disease. While each of these options is useful in particular clinical situations, none specifically addresses basic pathophysiology; corticosteroids, other immunosuppressive agents, and radiotherapy likely function as general immune suppressants, in part by inhibiting the production of cytokines and other inflammatory mediators by activated mononuclear cells. Likewise, transantral surgical decompression of the orbit mechanically relieves the increased pressure within the orbit by allowing the soft tissues to decompress into the maxillary sinus, but does not directly affect the autoimmune process.

The introduction of specific therapeutic and preventive strategies awaits a more complete understanding of the pathogenesis of Graves' ophthalmopathy. For example, therapies directed at neutralizing the stimulators of orbital fibroblast GAG production or modalities that inhibit the expression of immunomodulatory proteins by orbital fibroblasts might be useful. Therapies aimed at earlier steps in the disease process await a delineation of the relevant orbital antigens and of the T-cell epitopes involved. The understanding of basic mechanisms responsible for the association of eye disease, skin disease, and hyperthyroidism will solve a long-perplexing puzzle. More important, it will allow the development of preventive strategies or more effective therapies for our patients with this painful, disfiguring, and sight-threatening disease.

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Is Frequent Marijuana Smoking Harmful to Health?

OVER THE PAST quarter of a century, marijuana has remained the most commonly abused illicit drug in our society. According to the most recent national survey, more than 25% of high school seniors and young adults 19 to 30 years of age in the United States report having used marijuana within the past year, about 15% within the preceding month, and 2.2% to 2.5% (3.2% to 5.3% of young men) daily.[1] These figures probably underestimate the actual prevalence of marijuana smoking, since national surveys underrepresent high-school dropouts and young adults who are difficult to contact by mail, among whom drug use is likely to be greater than among those surveyed. Because smoking is the preferred route of the administration of marijuana and the smoke of marijuana contains a number of respiratory tract irritants and carcinogens,[2] there is justifiable concern that, as with tobacco, the habitual smoking of marijuana over years to decades can produce clinically substantial lung damage and respiratory tract malignancy.

This concern is supported by several experimental studies in animals[3-6] and in vitro[7-9] that have found considerable toxic, inflammatory, and even carcinogenic effects of exposure to marijuana smoke on lung tissue and cells. Until recently, however, few studies have examined the long-term pulmonary effects of real-life heavy, habitual marijuana smoking in humans. Early clinical studies of the respiratory consequences of habitual marijuana smoking published in the mid-1970s yielded conflicting results,[10-13] possibly because of small sample sizes and the failure to control adequately for confounding factors such as concomitant tobacco smoking. A more recent comparison study of 144 heavy, habitual smokers of marijuana only, 135 smokers of marijuana plus tobacco, 70 smokers of tobacco only, and 97 control nonsmokers revealed an association between heavy regular use of marijuana (3 to 4 joints per day for >5 years) and symptoms of acute and chronic bronchitis,[14] dysplastic and inflammatory changes in tracheobronchial mucosa,[15] increased numbers of alveolar macrophages and neutrophils in bronchoalveolar lavage fluid,[16] and impaired microbicidal activity of alveolar macrophages from marijuana smokers compared with tobacco smokers.[17,18] These findings indicate that frequent marijuana smoking can cause airway injury, lung inflammation, and impaired pulmonary defenses against infection. Results of other recent studies, moreover, have documented depressant effects of marijuana components on macrophage and human neutrophil function,[19,20] human natural killer cell activity,[21] and human mononuclear cell cytokine secretion,[22] suggesting that marijuana use increases the susceptibility to infection.

Several lines of evidence suggest that marijuana smoking is also associated with an increased risk for the development of respiratory tract malignancy:

- The insoluble particulate (tar) phase of the smoke from marijuana contains about 50% more of some carcinogenic aryl hydrocarbons, including benz[*a*]anthracene (a weak carcinogen) and benzo[*a*]pyrene (a strong carcinogen), than the smoke from a comparable quantity of unfiltered Kentucky reference tobacco.[2]
- The painting of smoke condensate (tar) from mari-

juana cigarettes on the skin of mice led to the development of metaplastic and neoplastic lesions that correlate with carcinogenicity.[2,23]

• Hamster lung explants exposed to marijuana or tobacco smoke over a period of two years led to atypical proliferation and disturbances in cell structural features and genetic equilibrium that were more impressive after marijuana than after tobacco exposure. These changes were followed by an accelerated malignant transformation within three to six months of marijuana exposure compared with that found in control explants.[8]

• In the Ames Salmonella-microsome test, marijuana smoke condensate induced a number of mutations comparable to those produced by an equivalent amount of tobacco tar.[24]

• Extensive metaplastic and dysplastic changes have been noted in the bronchial epithelium of heavy, habitual marijuana smokers who underwent biopsies at randomly selected sites of bronchial mucosa by fiberoptic bronchoscopy.[15] Squamous metaplasia and dysplasia are considered to be precursors of bronchogenic carcinoma.[25]

• Several cases have been reported of respiratory tract malignancy—tongue, tonsil, pyriform sinus, paranasal sinus, larynx, lung—in relatively young, long-term, habitual marijuana smokers.[26-30] Taylor identified 10 patients younger than 40 years out of 887 patients of all ages in whom respiratory tract cancer had developed: 2 of the lung—squamous cell carcinoma and small-cell anaplastic cancer—4 of the larynx, and 4 of the tongue. Interestingly, of these ten patients, five were heavy users of marijuana, two were regular marijuana smokers, one probably used marijuana, and the remaining two had no known history of use, implicating marijuana as an important cause of respiratory tract cancer, especially in persons younger than 40.

• The smoking of one marijuana cigarette—800 to 900 mg, 1% to 3% Δ^9-tetrahydrocannabinol—led to the deposition in the lower respiratory tract of about a fourfold greater quantity of insoluble smoke particulates (tar) than did smoking a filtered tobacco cigarette of comparable weight,[31] thus amplifying the exposure of the marijuana smoker to the carcinogens in the tar phase and increasing the risk of respiratory tract carcinogenesis.

Despite the evidence, which supports the view that habitual smoking of marijuana causes lung damage and predisposes to respiratory tract infection and malignancy, some advocates of the legalization of marijuana argue that marijuana is a far safer substance than tobacco. Advocates of marijuana "reform" contend that tobacco is responsible for hundreds of thousands of deaths each year due to cardiovascular disease and respiratory illness, whereas no definitive evidence exists linking marijuana, which is usually smoked in far smaller daily quantities than tobacco, to serious morbidity or mortality. The paucity of information concerning the health consequences of frequent marijuana smoking has been attributed, in part, to the relative recency of the upsurge in marijuana use prevalence and the lengthy lag period between possible long-term effects, such as respiratory tract malignancy and chronic obstructive pulmonary disease, and the initiation of use. Therefore, sufficient time may not have elapsed for these long-term health effects to become clinically obvious, particularly in view of the relatively small percentage of habitual daily smokers of marijuana who would appear to be at higher risk than the casual user. A long lag period should not be required for the expression of other harmful effects of marijuana, such as acute respiratory illness—bronchitis, pneumonia—although an epidemiologic assessment of the risk of marijuana smokers for respiratory tract infection developing is complicated by the potentially confounding influence of the concomitant use of other substances, including alcohol and tobacco. One might conclude from the dearth of information concerning marijuana-related morbidity either that such health effects are too infrequent to be measured or that such effects are occurring at greater than expected frequency but have not been documented because of the lack of a systematic effort to "capture" these events.

A crucially important obstacle to efforts to study the health effects of marijuana smoking in the "real" world is the nearly universal failure of physicians to query their patients concerning the use of marijuana. As pointed out by Polen and colleagues elsewhere in this issue of the journal, physicians recorded marijuana use in the medical records of only 3% of marijuana smokers who reported daily or near-daily smoking of marijuana in a comprehensive health survey.[32] These authors are the first to use a systematic review of medical records to assess the health consequences of marijuana, controlling for the effects of tobacco, alcohol, and sociodemographic variables. Their finding that near-daily marijuana smoking is a significant independent risk factor for the development of respiratory illness, injuries, and other medical problems requiring medical attention challenges the view that marijuana use poses insignificant health hazards. The authors appropriately acknowledge that their data are preliminary and that further study is required to evaluate the effects of marijuana smoking over a longer follow-up period and to examine dose-response relationships and interactions with tobacco and other substances of abuse.

Polen and co-workers have usefully pioneered the use of medical records as an epidemiologic tool for expanding our limited knowledge concerning the health consequences of the second most widely smoked substance in our society. The feasibility of this investigative strategy, however, depends on the diligence and consistency of physicians in incorporating into their routine history taking nonjudgmental questions concerning whether and to what extent their patients are using or have used marijuana, as well as other illicit drugs, and including this information in the medical record. Although more information is certainly needed, sufficient data have already been accumulated concerning the health effects of marijuana to warrant counseling by physicians against the smoking of marijuana as an important hazard to health. A physician's strong warning to patients informing them of what we do know about the harmful effects of marijuana

may persuade some of them, especially those with marijuana-related symptoms, to quit smoking.

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