Electronic Cigarettes

A Position Statement of the Forum of International Respiratory Societies

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Abstract

Background: Awareness and usage of electronic cigarettes has exponentially increased during the last few years, especially among young people and women in some countries. The rapid acceptance of electronic cigarettes may be attributed in part to the perception created by marketing and the popular press that they are safer than combustible cigarettes.

Goals: To alert and advise policy makers about electronic cigarettes and their potential hazards.

Methods: Using The Union's position paper on electronic cigarettes as the starting template, the document was written using an iterative process. Portions of the manuscript have been taken directly from the position papers of participating societies.

Results: Because electronic cigarettes generate less tar and carcinogens than combustible cigarettes, use of electronic cigarettes may reduce disease caused by those components. However, the health risks of electronic cigarettes have not been adequately studied. Studies looking at whether electronic cigarettes can aid smoking cessation have had inconsistent results. Moreover, the availability of electronic cigarettes may have an overall adverse health impact by increasing initiation and reducing cessation of combustible nicotine delivery products.

Conclusions: The health and safety claims regarding electronic nicotine delivery devices should be subject to evidentiary review. The potential benefits of electronic cigarettes to an individual smoker should be weighed against potential harm to the population of increased social acceptability of smoking and use of nicotine, the latter of which has addictive power and untoward effects. As a precaution, electronic nicotine delivery devices should be restricted or banned until more information about their safety is available. If they are allowed, they should be closely regulated as medicines or tobacco products.

Keywords: electronic cigarettes; nicotine delivery devices; tobacco products

Contents

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Overview

"Electronic cigarettes" or "electronic nicotine delivery systems" are devices that deliver to the lung vapors usually containing nicotine and other chemicals. The appeal to users and primary concern for health advocates is nicotine, which is highly addictive. Electronic cigarettes generate less tar and carcinogens than combustible cigarettes, but information sufficient enough to evaluate these products is lacking. Studies have shown that individuals who do not intend to quit smoking can reduce their intake of combustible cigarettes with electronic cigarettes, but other studies have failed to show superiority of e-cigarettes over nicotine replacement medicine or placebo for individuals trying to stop smoking. A public health concern is that the use of these products may increase the risk of nonsmokers developing nicotine dependence and of current smokers maintaining their dependence. The gravity of tobacco use on global health, the intensity of the nicotine addiction, and the historical behavior of the tobacco industry have prompted governments and health advocates to take a cautious approach to these products.

The position of the Forum of International Respiratory Societies (FIRS) on electronic nicotine delivery devices includes:

- The health risks of electronic cigarettes have not been adequately studied.
- The addictive power of nicotine and its untoward effects should not be underestimated.
- The potential benefits of electronic nicotine delivery devices, including harm reduction and as an aid to smoking cessation, have not been well studied.
- Potential benefits to an individual smoker should be weighed against harm to the population of increased social acceptability of smoking and use of nicotine.
- Health and safety claims regarding electronic nicotine delivery devices should be subject to evidentiary review.
- Adverse health effects for nonsmokers exposed to the emissions of electronic cigarettes cannot be excluded.
- Electronic nicotine delivery devices should be restricted or banned, at least until more information about their safety is available.
- If electronic nicotine delivery devices are permitted, they should be regulated as medicines and subject to the same evidentiary review as other medicines.
- If electronic nicotine delivery devices are not regulated as medicines, they should be regulated as tobacco products.
- Research, supported by sources other than the tobacco or electronic cigarette industry, should be performed to determine the impact of electronic nicotine delivery devices on health in a wide variety of settings.
- The patterns of use and the consequences at the population level of electronic nicotine delivery devices should be monitored.
- All information derived from this research should be conveyed to the public in a clear manner.

Introduction

"Electronic cigarettes" are devices that vaporize and deliver to the lungs a chemical mixture usually composed of nicotine, propylene glycol, and other substances. The appeal to users and concern from health advocates stems from the delivery of highly addictive nicotine via a noncombustible product. The devices are also referred to as "electronic nicotine delivery systems," although this is not precise because they can be engineered not to deliver nicotine. "Electronic cigarettes" is also not a precise term. Although most "electronic cigarettes" are shaped to look like their combustible tobacco counterparts (e.g., cigarettes, cigars, cigarillos, pipes, hookahs, or shishas), they may also be made to look like everyday items, such as pens and USB memory sticks, for people who wish to use the product without other people noticing (1). In this publication, we use terms "electronic cigarettes" and "electronic nicotine delivery devices" almost interchangeably, although "electronic cigarettes" is the more popular term for these devices and "electronic nicotine delivery systems" is the more formal, scientific, and legal term.

Electronic cigarettes were first produced in China in 2003 and are now available globally (2), However, the Legacy Tobacco Documents Library also showed that the Philip Morris company experimented with electronic cigarettes as early as the 1990s (3).

The devices contain an electronic vaporization system, batteries, electronic controls, and cartridges of the liquid that is vaporized. When activated by the user, the heating element vaporizes the liquid, which produces an aerosol that is inhaled. Electronic cigarettes almost always contain nicotine and flavorings. These may taste like candy and could be especially attractive to children or adolescents. Indeed, marketing of e-cigarettes has been directed at the young adults and children according to U.S. Food and Drug Administration documents (4).

Awareness and Prevalence of Use

In a short period, awareness has increased and use of electronic cigarettes has spread rapidly and extensively. In a consumer-based, mail-in survey of 10,587 adults in 2009 and 10,328 adults in 2010, awareness of electronic cigarettes doubled from 16.4% in 2009 to 32.2% in 2010. At the same time, the number of people who had tried electronic cigarettes more than quadrupled, from 0.6% in 2009 to 2.7% in 2010. Trying electronic cigarettes was common among women and those who were less educated, although these were not the groups who were most aware of them. Current smokers were most likely to use these devices (5). Similar increasing awareness and usage of electronic cigarettes also has been reported in other large surveys (6, 7).

A well-designed four-country survey reported the prevalence of electronic cigarette use in the United States, UK, Canada, and Australia (2). Overall, 46.6% of respondents were aware of electronic cigarettes (United States, 73%; UK, 54%; Canada, 40%; Australia, 20%). Of all persons surveyed, 7.6% had tried them, but 16% of persons who were aware of them had tried them. Overall, 2.9% were current users of e-cigarettes, but 39% of those who had tried them were current users. Younger persons, nonminority smokers, those with higher incomes, and heavier smokers were most aware of electronic cigarettes. Persons who were younger, had higher incomes, and perceived electronic cigarettes as being less harmful than combustible cigarettes were more likely to try them. In all, 79.8% of smokers who reported using electronic

cigarettes did so because they considered them less harmful than combustible cigarettes; 75.4% stated that they used them to reduce their smoking, and 85.1% reported using them to quit smoking (2).

The Global Adult Tobacco Survey 2011 for Indonesia showed that overall, 10.9% of adults were aware of electronic cigarettes, but only 0.3% used them (8). A recent review found that 10% of UK smokers used electronic nicotine delivery devices; the number of users rose to around 1.3 million in 2013, up from 700,000 the previous year (9).

In September 2013, the United States Centers for Disease Control and Prevention reported that e-cigarette use had doubled among middle and high school students from 2011 to 2012, resulting in an estimated 1.78 million students who had tried them by the end of 2012. Moreover, an estimated 160,000 students who reported trying electronic cigarettes had never used combustible cigarettes. Health authorities are concerned that nicotine may have a negative impact on adolescent brain development and increase the risk for nicotine addiction that could lead to the use of tobacco products (10). Increased use, especially among youth, has raised serious concerns about the overall impact of e-cigarettes on public health. Many public health and government groups have published statements or policies opposing or restricting their use. These have been reviewed in a statement by the International Union against Tuberculosis and Lung Disease (11).

Safety

The nicotine delivered in tobacco products is highly addictive and in relatively small amounts (0.5–1.0 mg/kg body weight for adults and 0.1 to 0.2 mg/kg for children) can be lethal. Manufacturers of e-cigarettes report that each replacement cartridge typically contains between 6 and 24 mg of nicotine, but some may contain more than 100 mg. To the degree that these products are not regulated or monitored, there is considerable variation in their contents, even within the same product (1, 9). Furthermore, the contents of these products are unknown to the consumer. Even if the product consistency became constant, the safety of electronic nicotine delivery devices has not been demonstrated (1, 12–14).

Replacement cartridges pose a risk for nicotine poisoning. For example, a 30-kg child who swallows the contents of a 24-mg nicotine cartridge is at high risk of developing acute and lethal nicotine poisoning (1). Nicotine, whether inhaled, ingested, or in direct contact with the skin, can be particularly hazardous to the health and safety of certain segments of the population, including children, young people, pregnant women, nursing mothers, people with heart disease, and the elderly. Cartridges and other refill accessories could be also ingested by young children and result in choking (15, 16).

Most electronic nicotine delivery devices contain large concentrations of propylene glycol, which is a known irritant when inhaled. Little is known about the health impact of long-term inhalation of propylene glycol. Tests by United States Food and Drug Administration revealed the presence of diethylene glycol, a chemical that has a history of mass poisonings and deaths when inadvertently substituted for propylene glycol in consumer products (17). The exact ingredients of electronic cigarettes are unknown, but the effects of ingredients that may be found in them should be identified and studied. This includes the effects of inhalation of irritants, solvents, genotoxins, and animal carcinogens (e.g., butyl acetate, diethyl carbonate, benzoic acid, quinoline, dioctyl phthalate 2,6-dimethyl phenol) (17). Because electronic cigarettes do not generate the smoke that is produced by combustion of tobacco, their use is commonly believed by consumers to be safer than smoking tobacco. However, the chemicals they contain have not been fully disclosed, and the safety is not assured.

Several studies involving human subjects (18–21) and other experimental models (22–24) underline concerns about toxicity, lack of safety information, and product design flaws that may have negative health consequences. These include the presence of toxic metals (cadmium, nickel, lead) and silicates in the e-cigarette vapor, although these are present at a lower level than found in combustible cigarettes (25). The current state of the design and manufacture of electronic nicotine delivery devices lacks quality control of toxic elements (26), nicotine dose (18), the presence of propylene glycol and other chemicals, and consistency of contents. The refill fluids may have cytotoxic effects on prenatal cells (22). There is limited information about the effects of electronic nicotine delivery systems on lung function (19). There is a lack of adequate labeling and absent or misleading information on product ingredients (20, 23). The sensation of inhaling e-cigarette aerosol may be less satisfying than from tobacco, leading to faster and deeper inhalation, which may also affect health adversely (21, 24). These issues have led experts to call for close regulation of electronic nicotine delivery devices (21).

Finally, there is concern that the material exhaled by users may be inhaled by others, especially indoors. Passive inhalation of the vaporized fine and ultrafine inhalable droplets and particles, nicotine, and cancer-causing substances into indoor air may have significant adverse health effects (27).

Harm Reduction of Electronic Cigarettes

The Premise

Electronic cigarettes do not produce the tar that is associated with tobacco smoke, which may be a major cause of bronchitis, emphysema, and lung cancer. Therefore, the premise is that replacing combustible with electronic cigarettes reduces the harm caused by combustible cigarette smoking. Furthermore, electronic cigarettes could be used as medical nicotine replacement products in promoting smoking cessation (28).

Health Effects of Nicotine

The harm-reduction premise ignores the deleterious effects of nicotine (29). Nicotine is highly addictive (30) and affects many body cells, mediators, and metabolic pathways (31). It has long been known to adversely affect children, not only *in utero* but also during postnatal development through adolescence. It may even cause adult disease. There is evidence that *in utero* exposure influences the later occurrence of conditions such as impaired fertility, type 2 diabetes, obesity, hypertension, neurobehavioral defects, and respiratory dysfunction (32). Nicotine has significant cardiovascular effects (33, 34) and may play a major role in the development of coronary artery

disease (35), atherosclerosis (36), and aortic aneurysms (37). Nicotine affects neuroregulation and structural changes in the brain and lung that could disturb a wide variety of reflexes and responses; these changes could increase vulnerability to hypoxia (38).

Nicotine has been associated with the development of peptic ulcer and gastrointestinal cancer (39), may promote tumor angiogenesis (40), and may alter neurologic development (41). Nicotine addiction may cause deleterious effects in women's brains by inhibiting estrogen signaling, which in turn may make the brain more susceptible to ischemia (42). There are many reports of the deleterious effect of nicotine on bones in both animal models and humans (43) and of the adverse effect of nicotine on chromosomes ("genotoxic effect") of fetal cells (44).

However, *medicinal* nicotine as an aid to smoking cessation has a good safety record. The doses of nicotine and its release mechanisms have been tested and standardized. These medicines have been approved by regulatory agencies after extensive study. The hazards of electronic cigarettes are that they have not been adequately tested, standardized, or regulated as nicotine delivery systems, and, therefore, their safety is uncertain.

Electronic Cigarettes as an Aid to Smoking Cessation and Tobacco-Use Reduction

Studies of the effectiveness of electronic cigarettes as an aid to smoking cessation differ from studies that have an endpoint of reducing tobacco use. In a study designed to evaluate smoking reduction and abstinence in 300 smokers who did not intend to quit, two different nicotine strengths of a popular Italian e-cigarette model (Categoria; Arbi Group s.r.l., Rivanazzano Terme, Italy) were compared with a nonnicotine e-cigarette. All three groups had a reduction in the number of combustible cigarettes smoked per day, and there was no consistent difference between groups. There were no significant side effects (45). The same authors also published a prospective, observational study that found more than a 50% smoking reduction, also in smokers who did not intend to quit. However, 17 of the 40 subjects were lost to follow-up at 24 months. Despite the 42% drop-out rate, the investigators concluded that long-term e-cigarette use is well tolerated and can substantially decrease combustible cigarette consumption in smokers not planning to quit (46).

In a controlled trial conducted in New Zealand, 657 smokers were randomized (289 to nicotine e-cigarettes, 295 to nicotine patches, and 73 to placebo e-cigarettes) and compared with an intention-to-treat analysis. At 6 months, verified abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8% (17 of 295) with patches, and 4.1% (3 of 73) with placebo e-cigarettes. The relative risk of achieving abstinence for nicotine e-cigarettes was 1.51 compared with nicotine patches and 3.16 compared with placebo. Achievement of abstinence was substantially lower than the researchers anticipated for the sample size calculations. Thus, the study was not able to conclude superiority of nicotine e-cigarettes to patches or placebo, nor did it show significant differences in adverse events among the groups (47).

A cross-sectional survey of 1,836 current or recently quit adult smokers found that 38% had tried an alternative tobacco product, most frequently electronic cigarettes, but the electronic cigarettes were not associated with successful quit attempts (48). A survey of 3,240 individuals, which found never smokers and former smokers had tried these products, concluded with concern that electronic cigarettes could increase the risk of nonsmokers developing nicotine dependence and of current smokers maintaining their dependence (49).

The four-country survey, cited earlier, found nearly three-fourths (70.4%) of those sampled used electronic nicotine delivery devices to obtain nicotine in smoke-free spaces, indicating that electronic cigarettes were being used also to satisfy nicotine addiction during periods of temporary cigarette smoking abstinence. Current electronic cigarette use was associated with a greater reduction in cigarettes per day over time, compared with those who did not use them. However, electronic cigarettes users were not more likely to quit smoking than those who did not use them (2).

Other studies have not shown significant benefit of using electronic nicotine delivery devices for smoking cessation (50, 51).

Comparative Effect versus Combustible Cigarettes

Current information suggests that for an individual, use of electronic cigarettes would reduce overall health risk compared with smoking combustible cigarettes (52). However, for a population, the availability of electronic cigarettes may have an overall adverse impact by increasing initiation and reducing cessation of smoking (29). Electronic cigarettes could lead to an increase in nicotine use and dependence and be a gateway to combustible tobacco products. Alternatively, electronic cigarettes could lead to a reduction in combustible cigarette use among established smokers, potentially leading to incremental health benefits regarding tobacco-related morbidity. More study is needed, with careful tracking of what is happening in populations where electronic cigarettes are available.

Regulation and Legislative Responses to Electronic Cigarettes

The gravity of the adverse effects of tobacco use on global health (53) and the historical behavior of the tobacco industry that has included deceit about the health effects of tobacco, intentional marketing to children, and manipulating nicotine levels in cigarettes to maintain or increase addiction (54) has prompted governments, health officials, and health advocates to monitor and censure the tobacco industry. The tobacco industry has spent enormous sums of money and manipulated information to influence health-care policy through its advertising strategy (55). It has misleadingly marketed filtered and "low-tar" cigarettes as "healthier" and "safer" alternatives without adequate scientific evidence. Use of these products inevitably resulted in untold suffering and premature death for millions of people worldwide. Because nicotine is central to the lifelong addiction, and because these are nicotine delivery instruments, careful investigation and regulation of these products are required.

Many governments have chosen to restrict the sale of nicotine delivery systems or to ban them entirely. On February 26, 2014, the European Commission Directive issued a strong statement about electronic cigarettes and their safety (56). Electronic cigarettes and other electronic products containing nicotine are to be regulated as medicines in the UK from 2016 onward; the move comes after an investigation into the products by the Medicines and

Healthcare Products Regulatory Agency (57). However, the Agency's plans are aligned with forthcoming European legislation stipulating that electronic nicotine delivery devices would not be required to obtain a medicine license until the European Commission's Tobacco Products Directive agrees. The revision of the European Commission's Directive is expected to address the following main issues:

- how to regulate products that do not contain tobacco but are closely linked to smoking or tobacco consumption, such as electronic and herbal cigarettes;
- labeling and packaging of tobacco products;
- additives, such as flavorings, used in tobacco products;
- internet sales of tobacco products; and
- tracking the use of these products.

This contrasts with actions in other countries that introduced restrictions on the sale and use of electronic nicotine delivery devices. Brazil, Norway, Singapore, and Indonesia have banned them completely (57); the Food and Drug Monitoring Agency of Indonesia has warned that electronic cigarettes could be more dangerous than combustible cigarettes (58).

In the Philippines, the Food and Drug Administration issued an advisory notice on secondary exposure to electronic nicotine delivery device emissions. Citing the review published by the German Cancer Research Centre (27), the advisory states that the possibility that "Second-hand exposure to e-cigarette emission which may lead to adverse health effects cannot be excluded." It goes on to recommend that, "The public, especially the youth sector, is advised NOT to start smoking at all and to stop using cigarettes, cigars or e-cigarettes." The Consumer Act of the Philippines strengthened local ordinances against smoking in public places and on second-hand exposure to harmful substances (59, 60).

On April 24, 2014 the United States Food and Drug Administration (FDA) Center for Tobacco Products proposed regulations that would ban the sale of electronic cigarettes to minors and require manufacturers to register with the FDA and give a detailed accounting of the ingredients. The packages would have to have labels warning that nicotine is addicting, but the rules would not outlaw flavors or advertising (61).

World Health Organization Framework Convention on Tobacco Control

The Framework Convention on Tobacco Control is a treaty developed by the World Health Organization and the World Health Assembly in 2003 to control tobacco use worldwide (62). The treaty came into force in 2005 and is legally binding in the 178 ratifying countries. It is updated regularly, and the Conference of the Parties to the treaty published a report in June 2012 inviting further comment on electronic nicotine delivery systems including electronic cigarettes (60). It concluded that the popularity of electronic nicotine delivery devices was growing rapidly, that health and safety concerns have not been resolved, and that more research must be conducted, especially with regard to the safety of these devices and the marketing claims made by the manufacturers.

Additional concerns were that electronic cigarettes resemble combustible cigarettes and could undermine the denormalization of tobacco use that is an important tenet of tobacco control. A guiding principle for implementation of the Framework Convention is to use education, communication, training, and public awareness "to change social, environmental and cultural norms and perceptions regarding the acceptability of the consumption of tobacco products, exposure to tobacco smoke..." (62).

The producers of electronic cigarettes have spent large sums in advertising to portray "vaping" as a socially acceptable and desirable activity. A ban of electronic nicotine delivery devices could turn back this advertising movement, which aims to change the social norms to favor consumption of these "tobacco-like" products.

If electronic nicotine delivery devices are regarded as imitation tobacco products and banned, then all electronic nicotine delivery devices would be covered, regardless of whether or not they contain nicotine or tobacco extracts. The Framework already has provisions, such as Article 5.2(b), which requires parties to the treaty to "adopt and implement effective . . . measures . . . for preventing and reducing . . . nicotine addiction" (62). This article could potentially mandate a ban on electronic nicotine delivery devices that contribute to maintaining addiction to nicotine.

Furthermore, under Article 13.2, parties to the treaty have an obligation to undertake a comprehensive ban of all tobacco advertising, promotion, and sponsorship. Therefore, parties to the treaty may also consider whether the sale, advertising, and even the use of electronic cigarettes could be considered as promoting tobacco use, either directly or indirectly. Regardless of whether or not electronic nicotine delivery devices contain nicotine or tobacco extracts, they are used to mimic smoking, which could be considered as a (direct or indirect) promotion of tobacco use. Article 16.1(c) could also be relevant because it requires parties to prohibit "the manufacture and sale of . . . any other objects in the form of tobacco products which appeal to minors" (62).

Additionally, the use of electronic nicotine delivery devices could be conceived as counter to Article 8 (Protection from exposure to tobacco smoke), which protects individuals in public places, because electronic cigarettes produce emissions that can be regarded as second-hand smoke.

If electronic nicotine delivery devices are not banned, the strategy of the Framework could be to regulate them as both a tobacco and a medical product and close loopholes in their regulation. If electronic cigarettes are marketed with therapeutic or health claims, they should be regulated as medical products and be subject to the Framework's relevant regulations, most notably the requirement to provide data substantiating those claims to obtain market authorization. If the Framework parties decided to categorize and regulate electronic nicotine delivery devices as tobacco products, all provisions of the tobacco part of the Framework would apply.

FIRS Positions on Electronic Nicotine Delivery Devices

The FIRS has the following positions and concerns on electronic nicotine delivery devices:

- There is concern that the use of electronic cigarettes is growing rapidly, especially among young people and

women. Their acceptance may be attributed in part to the perception created by marketing and the popular press that they are safe.
- The health risk of electronic cigarettes has not been adequately studied.
- The addictive power of nicotine and its untoward effects should not be underestimated.
- The potential benefits of electronic nicotine delivery devices, including harm reduction and enhancing smoking cessation, have not been adequately studied.
- Potential benefits to an individual smoker should be weighed against harm to the population of increased social acceptability of smoking and use of nicotine.
- Health and safety claims regarding electronic nicotine delivery devices should be subject to evidentiary review.
- Adverse health effects for third parties exposed to the emissions of electronic cigarettes cannot be excluded.
- Parties to World Health Organization Framework Convention on Tobacco Control should consider whether allowing use of electronic cigarettes is consistent with the requirements of the treaty.
- Electronic nicotine delivery devices should be restricted or banned, at least until more information about their safety is available.
- In the absence of a ban, we recommend that devices that deliver nicotine be regulated as medicines. This includes the prohibition of their promotion for tobacco-use cessation and other health effects until there is strong evidence that establishes their benefits and lack of harm as is required by regulatory agencies for approval of other medicines.
- If electronic nicotine delivery devices are not regulated as medicines, they should be regulated as tobacco products. This includes: (*1*) a ban on all advertising, promotion and sponsorship; (*2*) prohibition of displays in retail stores; (*3*) prohibition of sale to minors; (*4*) regulation of internet sales; (*5*) taxation at rates similar to combustible cigarettes; (*6*) prohibition of sales and refills with flavors that will appeal to children; (*7*) requirement that packaging and labeling include a list of all ingredients and the quantity of nicotine; (*8*) placement of appropriate warning labels, the same as is required for tobacco products; and (*9*) prohibition of their use in public places, workplaces, and on public transportation.
- In the absence of a ban, manufacturers of electronic cigarettes should adhere to established consumer safety practices that list ingredients and produce consistent products with uniform concentrations and defined maximum doses of nicotine. They must safeguard against inadvertent poisonings, which includes child-proofing containers and other protections.
- Research supported by sources other than the tobacco or electronic cigarette industry should be performed to determine the impact of electronic nicotine delivery devices on health in a wide variety of settings.
- The use and population effects of electronic nicotine delivery devices should be monitored.
- All information derived from this research should be conveyed to the public in a clear manner.

Conclusions

Electronic cigarettes are nicotine delivery devices that have rapidly gained popularity because of marketing and the belief that they are safe and helpful for cessation of cigarette smoking. The health risks of these products, however, have not been adequately studied. Because nicotine is highly addictive, affects many bodily cells and functions, and is known to have many adverse effects, it is prudent to restrict usage of these products at least until their safety can be established. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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