A Comparative Study of the Pulmonary Mycoses of Canada and the United States

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A COMPARATIVE study of the pulmonary mycoses of Canada and the United States shows a basic similarity in the types of diseases that occur in these two countries. Coccidioidomycosis is the only systemic mycotic disease that is present in one country (the United States) and not in the other. All the other mycoses are shared; however, there are significant national differences in their prevalence and incidence.

This paper describes, from an epidemiologic point of view, the pulmonary mycoses that prevail in these two northern countries. The diseases are discussed under two categories: endogenous and exogenous infections.

Endogenous Pulmonary Mycoses

In the category of endogenous pulmonary mycoses are the mycoses caused by organisms that are not known to be free-living in nature but are normal components of the body's microflora. The two diseases caused by such organisms are actinomycosis and candidiasis.

Actinomycosis. Human actinomycosis is caused exclusively by *Actinomyces israelii.* Until recently this organism had been confused with *Actinomyces bovis*, the etiological agent of bovine actinomycosis, but these two closely related anaerobic actinomycetes have been proved to be separate and distinct species on the basis of their antigenic and biochemical properties (*1*, *2*).

There are no acceptable records of the recovery of *A. israelii* from soil or any inanimate source. This actinomycete appears to be uniquely adapted to live as a commensal in the human oral cavity. It is assumed that early in life this highly specialized anaerobe is transferred from parent to child and becomes established in the infant's oral cavity. In a recent survey that used specific fluorescent antibody procedures for identification, 30 tonsils out of 116 (26 percent) obtained from routine tonsillectomies contained *A. israelii* (*3*).

Despite the high prevalence of *A. israelii* infestation among human beings, the number of active clinical cases of pulmonary actinomycosis that develop yearly is believed to be low. But since the mycoses are not notifiable diseases, we do not really know how many cases of pulmonary actinomycosis do occur. In recent years, few cases have been reported from Canada and the United States.

The circumstances that sever the apparently innocuous relationship between *A. israelii* and man are not known; however, aspirations of *A. israelii* cells and granules from the oral cavity as well as lowered host resistance may be two factors.

Candidiasis. The fungus *Candida albicans* is the most frequent cause of human primary and secondary candidiasis. This yeast is a well-known commensal of the human normal oral

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cavity, intestine, and vagina (*4*). *C. albicans* becomes established in our bodies at birth during passage through the birth canal. Rarely, infections may have an intrauterine origin (*5*, *6*).

C. albicans is a notorious opportunistic fungus. The delicate relationship that keeps this fungus innocuous can be upset by many factors. The protracted administration of antibiotics, corticosteroids, or immunosuppressants as well as heavy doses of X-ray and cobalt irradiation so often interferes with defense mechanisms that candidiasis develops in the lungs and other organ systems. Debilitating bacterial and malignant diseases also permit *C. albicans* to become invasive and cause severe secondary infections. As a result, opportunistic infections caused by *C. albicans* have increased tremendously (*7*, *8*), not only in Canada and the United States but throughout the world. Thus, in the differential diagnosis of pulmonary diseases, it is imperative that the possibility of primary or secondary infections caused by *C. albicans* be considered. An arbitrary decision that *C. albicans* is a contaminant of clinical materials, especially of blood, body fluids, and sputum from patients with bronchopulmonary diseases, could prove to be disastrously tragic for a patient.

Although many species of lower animals harbor *C. albicans*, they are not known to take part in the transmission of infection to man. *C. albicans* is occasionally isolated from inanimate sources in nature (*9*, *10*), but this is not considered indicative of a saprophytic existence. Its presence in these substrata is best interpreted as a transitory one resulting from animal and human contamination.

Exogenous Pulmonary Mycoses

All the diseases caused by aerobic actinomycetes and fungi that exist or are presumed to exist as saprophytes in nature are exogenous pulmonary mycoses. Most of the systemic mycoses fall into this category. The following discussion includes aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis.

Aspergillosis. Aspergillus fumigatus is the predominant cause of aspergillosis within the United States and Canada. This fungus is widespread in nature where it exists as a saprophyte on a wide variety of nonliving substrata (*9*). It is surprisingly abundant, especially in decomposing vegetation which yields visible clouds of spores when stirred (*10*).

Other species of aspergilli occasionally cause pulmonary infections. Members of the following groups have been incriminated: *Aspergillus flavus*, *Aspergillus nidulans*, *Aspergillus niger*, and *Aspergillus terreus* (*9*, *11*). These fungi are also widely distributed in nature as saprophytes, where they are significant in the decomposition of organic matter. Some of the members of the groups mentioned possess latent abilities to grow in animals and cause disease.

Aspergillus spores are produced in such great numbers that they are frequently isolated from the air. Spore counts have varied from 600 per cubic meter in the open air to 2,300 per cubic meter in a hospital ward and an impressive 12 to 21 million per cubic meter in barns (*9*).

Aspergillosis occurs in man through the inhalation of spores. However, mere inhalation of spores even at high dosage levels does not generally result in infection. Predisposing factors that inactivate or reduce the efficacy of the host's defense mechanisms are needed before aspergillus spores germinate and begin to invade the tissues of the host.

Although aspergillosis is a common disease of lower animals, there is no reason to believe that they transmit it to man.

Data on the prevalence of aspergillosis in Canada and the United States are not available. However, the disease is not rare, and in this era of therapy with antibiotics, corticosteroids, and immunosuppressive drugs that alter resistance mechanisms, more and more cases of aspergillosis are being recorded (*7*, *12*).

A word of caution is needed regarding the significance to be placed on the isolation of aspergilli from clinical materials. Isolation alone does not constitute *prima facie* evidence of infection. Many isolates merely represent inhaled spores that persisted in the mucous lining of the respiratory apparatus and were coughed up by the patient and cultured. Interpretation of the recovery of basically saprophytic fungi in a diagnostic situation must always be correlated with the clinical status of the patient and other laboratory findings.

Blastomycosis. Blastomycosis is caused by *Blastomyces dermatitidis*, a fungus long

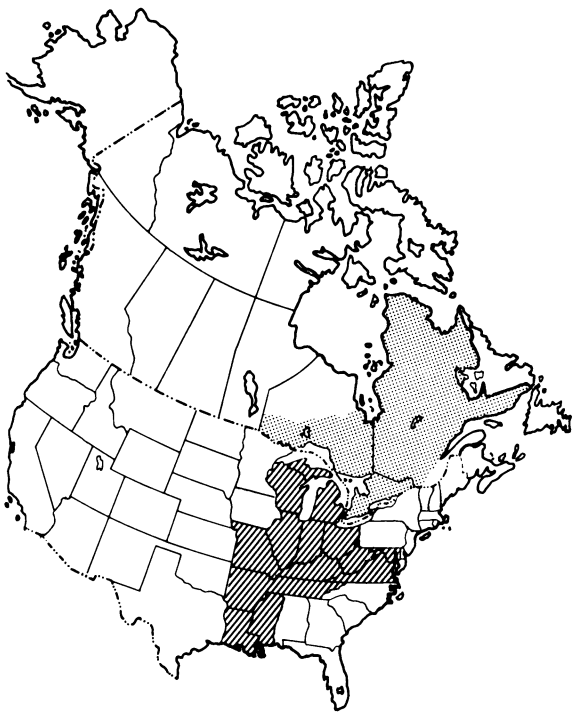

Figure 1. Blastomycosis endemic areas in Canada and the United States

thought to be geographically restricted to North America. But a growing number of autochthonous cases of blastomycosis have been diagnosed in Africa (*13*). In addition, there is some tenuous evidence that the disease exists in Latin America (*13*). But the vast majority of cases have been reported from the United States and to a lesser extent from Canada.

The endemic areas in these two countries are essentially confined to their eastern portions (fig. 1). In Canada most cases have been reported from the Provinces of Ontario and Quebec (*14*). Eastward, only three cases have been noted—two in New Brunswick and one in Nova Scotia. To the west, Manitoba (eight cases) and Saskatchewan (one case) are the only other Provinces with recorded cases of blastomycosis.

Within the United States the endemic area centers in the States of Arkansas, Kentucky, Louisiana, Mississippi, North Carolina, and Tennessee (*15*, *16*). Radially from these States the number of cases diminishes radically toward the northeast, southeast, and west. Appreciable numbers of cases have been recorded only in the States north of this region: Illinois, Indiana, Iowa, Michigan, Minnesota, Missouri, and Wisconsin.

Information on the endemic areas of blastomycosis depends on case records because of the present inadequacy of blastomycin, the skin-testing antigen. This crude preparation lacks specificity and potency and therefore cannot be used in determining and mapping sensitivity levels in the general population. We also remain ignorant of the possible existence of a benign subclinical form of blastomycosis.

The predominant victims of blastomycosis are 30- to 50-year-old men. The ratio of male-to-female cases is variously estimated to range from 6:1 to 15:1 (*16*, *17*). There seem to be no differences in racial susceptibility (*15*), and the majority of cases have occurred in persons who work close to the soil.

Such observations, coupled with indications that blastomycosis is primarily a pulmonary disease acquired through the inhalation of airborne spores, lead to the belief that *B. dermatitidis* exists in nature as a saprophyte. In fact, isolations of *B. dermatitidis* from soils collected in Georgia and Kentucky have been reported (*18*, *19*). However, these findings need to be duplicated and extended before the natural habitat of *B. dermatitidis* can be discovered and characterized. This statement is based on the puzzling nature of the positive soils and collection sites that yielded the fungus only once. Repeated culturings of a once "positive" specimen failed to yield the fungus again. Similarly, additional specimens from the original "positive" site always proved negative.

Blastomycosis in lower animals is frequent, and the dog appears to be the most susceptible. In the United States more than 180 cases in dogs have been reported (*20*, *21*); the States with the highest prevalence were Arkansas, Illinois, Iowa, and Kentucky. Only three cases of blastomycosis in dogs have been reported from Canada.

Interestingly, the only other lower animal victims of *B. dermatitidis* have been a horse in Iowa (*22*) and a Steller's sea lion (*Eumetopias jubata*) held captive in an Illinois zoo (*23*).

Despite the high prevalence of canine blastomycosis, there is no evidence that the infection is transmitted to man. Nor is there reason to sus-

pect transference of the disease from one person to another.

Coccidioidomycosis. Coccidioidomycosis is the one systemic mycotic disease present in the United States that is not native to Canada. The etiological agent *Coccidioides immitis* is a highly specialized soil organism found only in the semiarid regions of the United States and Latin America.

According to Maddy (*24*) the conditions to which *C. immitis* is superbly adapted are "an arid or semiarid climate, alkaline soil, relative freedom from severe frosts and a very hot dry season of several months, followed by some rain. July mean temperatures from 26°C. to about 32°C., January mean temperatures from 4°C. to about 12°C., and an annual rainfall of about 5 to 20 inches." Such conditions are found in suitable portions of Arizona, California, New Mexico, Nevada, Texas, and Utah (fig. 2). In these areas during the extended periods of extreme heat and aridity, *C. immitis* survives just below the uninhabitable hot surface of the soil or in rodent burrows. After the rainy season, it reinvades the surface where in a partially sterilized environment it sporulates heavily. Then, as the soil dries, winds pick up the highly infectious spores and disseminate them into the air.

The airborne spores are inhaled by people and lower animals and give rise to infections. The clinical spectrum of coccidioidomycosis ranges from a benign asymptomatic form to an acute pulmonary mycosis that may be self-limited or that disseminates and affects all vital organs.

An estimated 60 percent of all *C. immitis* infections are asymptomatic. Persons with this form of the disease do become sensitized to the antigens of *C. immitis* and thus their sensitivity can be detected by coccidioidin, the skin-test antigen. This antigen is invaluable for use in discovering and delimiting endemic areas and in determining levels of infection in the general population.

There is strong immunological evidence that infections by *C. immitis* not only induce hypersensitivity and the development of humoral antibodies but confer a certain degree of immunity to reinfection. This latter phenomenon has led to the development of experimental vaccines

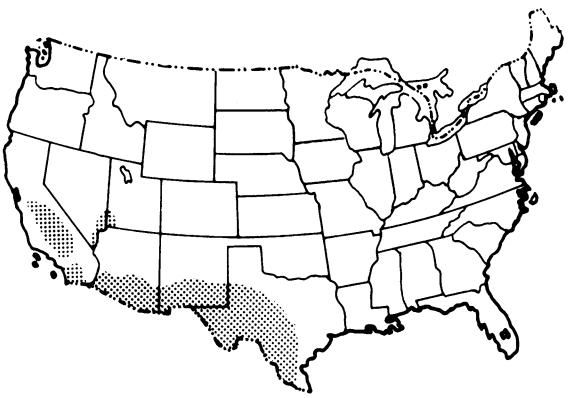

Figure 2. Coccidioidomycosis endemic areas in the United States

against coccidioidomycosis (*25*). These hold high promise and, when perfected and fully evaluated, may be of great value in protecting high-risk groups. In the interim, preventive measures center around dust abatement programs including planting of grass and oiling of exposed ground areas.

Although a wide variety of domesticated and wild animals are infected by *C. immitis* (*13*), there is no evidence that coccidioidomycosis is transmitted from animals to man or from man to man. All infections are traceable to a common source—soil.

Several cases of coccidioidomycosis have been diagnosed in Canada (*26–29*). These cases, however, occurred in persons who had either traveled to or worked in the endemic areas of Mexico and the United States and became infected there (*27–29*) or had apparently come in contact with materials contaminated with *C. immitis* exported from the United States (*26*).

The Canadian cases illustrate the need for public health workers to be prepared to diagnose diseases that occur far from their points of origin.

Cryptococcosis. Cryptococcosis, unlike blastomycosis and coccidioidomycosis, is a cosmopolitan disease. Cases have been reported from all parts of the world. It is caused by the imperfect yeast *Cryptococcus neoformans*, which lives as a saprophyte in soil.

Ecological studies carried out by Emmons (*30*) first revealed a significant relationship between pigeons (*Columba livia*) and *C. neoformans*. This fungus was isolated from 63 of

111 (63 percent) pigeon nests. Subsequent surveys of pigeon and other bird nests and droppings, carried out by investigators throughout the world, have confirmed this association (*13*). The role of birds in the ecology and epidemiology of cryptococcosis is believed to be indirect, since spontaneous avian infections have yet to be diagnosed.

Staib (*31*, *32*) has provided an apparently logical explanation for the affinity of *C. neoformans* to bird dung. His studies showed that bird manures serve as enrichment media for *C. neoformans* by virtue of their chemical makeup. Staib postulated that creatinine, one of the constituents of bird urine, can be assimilated by *C. neoformans* but not by other cryptococci and yeasts of other genera. Thus there is an apparent biochemical basis for the frequency of *C. neoformans* in avian habitats.

Striking concentrations of *C. neoformans* undoubtedly exist in our environment. Some pigeon manure studied by Emmons (*10*) contained 50 million viable cells of this yeast per gram of dried material. However, the prevalence of infections among the general population is unknown. Lack of a specific and sensitive antigen precludes determination of sensitivity to *C. neoformans* in population groups. Educated guesses regarding the incidence of cryptococcosis in the United States range from 200 to 300 cases of cerebral meningitis per year for the country as a whole (*33*) to a rate of 5,000 to 15,000 cases of subclinical or clinical pulmonary cases in New York City alone (*34*). Deaths attributed to *C. neoformans* in the United States have averaged 72 per year during the 10-year period of 1957–66 for a total of 724 (*35*). Comparable data on Canada are not available. Based on the few cases reported, however, it appears that cryptococcosis may be a rare disease in Canada (*36–41*).

C. neoformans has been observed in a wide variety of mammals (*13*), but there is no evidence that animals are directly involved in the transmission of cryptococcosis to man. Cryptococcosis is an airborne disease with soil as the ultimate source of infection.

Histoplasmosis. In the United States and Canada histoplasmosis is undoubtedly the most prevalent of all the systemic mycoses caused by exogenous fungi. Based on extensive skin-test surveys, an estimated more than 30 million U.S. inhabitants have been infected by *Histoplasma capsulatum* (*42*). In some of the endemic areas, more than 90 percent of the residents have positive reactions to histoplasmin (*43*).

The high prevalence of infections in the United States is reflected in the number of fatalities attributed to histoplasmosis. An average of 75 deaths per year has been recorded over the 10-year period from 1957 to 1966, for a total of 746 (*35*).

Yearly, hundreds of patients with acute, disseminated, and chronic histoplasmosis require hospitalization. A search for histoplasmosis among patients in tuberculosis sanatoriums throughout the United States led to the conclusion that as many as 8,200 patients with serologic evidence of histoplasmosis are admitted to such institutions. One-fourth of these patients or 2,050 could be proved to have active cases of histoplasmosis by culture procedures (*44*).

Based on skin-test surveys and casefinding, it is known that the principal U.S. area in which histoplasmosis is endemic is located in the Mississippi-Ohio River valleys (fig. 3). This en-

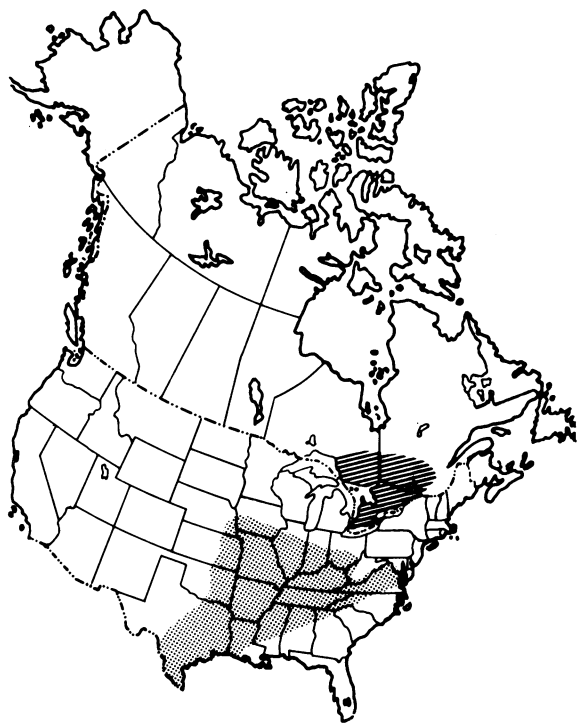

Figure 3. Histoplasmosis endemic areas in the United States and Canada

compasses all or parts of Arkansas, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Ohio, Oklahoma, Tennessee, and Texas. In these States the prevalence of histoplasmin sensitivity ranges from 40 to 90 percent (*43*). Beyond these States, sensitivity levels drop or may be virtually absent in the general population. But there may be foci of relatively high sensitivity levels in localized areas such as occur in Georgia (*45*), Iowa (*46*), Michigan (*47*), and New York (*48*).

In contrast to the United States, the incidence and prevalence of histoplasmosis in Canada is relatively low. As shown in table 1, histoplasmin surveys have revealed sensitivity levels ranging from 0 to 68 percent among selected regional groups (*49*, *50*). The highest rates, however, with the exception of St. Thomas, occurred among persons who had traveled outside of Canada and may have become sensitized elsewhere. In Canada the Provinces of Ontario and Quebec seem to be the areas with the highest prevalence of autochthonous infection. This concentration is confirmed by the geographic distribution of the relatively few reported cases of acute and fatal Canadian histoplasmosis. All cases of this type, confirmed by histological or culture findings, originated in those two Provinces (*50–66*). The only lower animal case reported was in a dog in Ontario (*67*).

Ecological investigations have incontrovertibly established that *H. capsulatum* is a soil fungus that flourishes as a saprophyte in avian and chiropteran habitats. In the United States and elsewhere, such studies have shown that this fungus is most frequently recovered from soils enriched with the excreta of bats and birds (*13*). It is believed that the chemical components of those soils give *H. capsulatum* a competitive advantage over other organisms. But climatic and other factors must also operate in the distribution and occurrence of this fungus in nature. *H. capsulatum* is not found in all bat and bird habitats. The ecological factors that essentially restrict it to specific habitats within certain regions are complex, and intensive studies will be required before they can be defined. As yet, there are no records of the recovery of *H. capsulatum* from Canadian soil.

The role of bats in the epidemiology of histo-

Table 2. U.S. species of bats infected by *Histoplasma capsulatum*

Bat species	Locality
Eptesicus fuscus (big brown bat)	Indiana, Maryland, Tennessee.
Leptonycteris sanborni (long-nosed bat).	Arizona.
Myotis austroriparius (southeastern myotis).	Florida.
Myotis grisescens (gray myotis)	Alabama, Tennessee, Virginia.
Myotis lucifugus (little brown bat).	Indiana, Montana.
Myotis sodalis (Indiana myotis)	Tennessee.
Nycticeius humeralis (evening bat).	Mississippi.
Tadarida cynocephala (Florida free-tailed bat).	Alabama.
Tadarida brasiliensis mexicana (Mexican free-tailed bat).	Arizona, Texas.

SOURCE: reference 70.

Table 1. Prevalence of histoplasmin sensitivity in Canada

Area surveyed	Study group	Number tested	Percent positive
Abitibi (east), Quebec	Indian population	161	5
Beloeil, Quebec	School children	75	27
Elgin County, Ontario	General population	3, 364	29
Halifax, Nova Scotia	University students	310	1
Kingston, Ontario	do	(1)	20–30
Montreal, Quebec	Chest clinic patients	100	21
Newfoundland	General population	157	0
Saint Agathe des Monts, Quebec	Tuberculosis sanatorium patients	270	10
Saint Thomas, Ontario	Residents	230	68
Toronto, Ontario	University students without calcification	134	10
Do	do	63	57
Winnipeg, Manitoba	Hospital patients	440	5

[1] Not stated.

SOURCES: references 49 and 50.

plasmosis remains unknown. These flying mammals, in contrast to birds, are susceptible to histoplasmosis (*68*, *69*). As shown in table 2, *H. capsulatum* has been isolated from nine species of bats in the United States (*70*). This has led to ill-founded speculation that bats are active in the epidemiology of histoplasmosis (*71*). There is no basis for statements such as "the bat is the source of the infective agent" or "it is reasonable to predict that an increase can be expected in the number of microfoci of *H. capsulatum* in nature and possibly in geographic areas in which the disease has not heretofore been found." *H. capsulatum* evolved long ago, and undoubtedly was present in the New World in suitable ecological habitats that were established and invaded in prehistoric times. The geographic distribution of *H. capsulatum* does not seem to be correlated with that of bats.

Bat surveys are useful in discovering new foci of infestation and in determining the prevalence of the fungus in a given area. Their value as an epidemiologic tool became evident when cave bats were collected and cultured for *H. capsulatum* in Florida and Arizona. Although both States have been considered outside the endemic areas of histoplasmosis, positive bats were found (*69*, *70*, *72*). It is evident that microhabitats suitable for *H. capsulatum* exist beyond the borders of the classic endemic areas.

Many genera and species of mammals besides bats are infected by *H. capsulatum* (*13*). But as with the other deep mycoses, there is no evidence of transmission of the disease to man.

Numerous outbreaks of acute pulmonary histoplasmosis with occasional fatalities among persons who inhaled airborne spores of *H. capsulatum* that arose from disturbed avian habitats have been recorded and have led to the development of control measures (*47*, *48*, *73*). Field trials with repeated applications of 3 percent formalin eliminated *H. capsulatum* from the surface of a naturally infected area (*74*); 233,000 gallons of formalin were applied to a 5-acre site at a cost of $4,000. This amount of formalin approximated 1.7 inches of rainfall. During a 10-month followup, *H. capsulatum* was not isolated from the surface of the sterilized area.

Other methods have been tested and evaluated (*75*, *76*). One most economical yet effective control measure is the overlaying of an infested site with 6 to 8 inches of soil which is free of *H. capsulatum* (*75*). A combination of fungicides and soil overlays may prove to be the most effective procedure for eliminating the danger of infections in circumscribed sites.

Conclusions

With the exception of coccidioidomycosis, Canada and the United States share the same pulmonary mycoses; however, there are significant differences in their incidence and prevalence.

Lack of suitable habitats for the survival and growth of *C. immitis* undoubtedly accounts for this organism's absence from Canada. Canada simply does not possess a climate that creates and maintains semiarid regions similar to those of the North American southwest in which *C. immitis* flourishes.

Climatic differences may also account for the disparity in the extent of *B. dermatitidis* and *H. capsulatum* infections in the two countries—a high infection rate in the United States and a relatively low infection rate in Canada. But the systemic mycoses do take a heavy toll of lives and have high morbidity rates; thereby, they constitute a serious public health problem. Knowledge of the epidemiology of these diseases, when applied judiciously for control purposes, will reduce their incidence.

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