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Legionnaires' disease: an illness whose time has come

Since the first documented outbreak of Legionnaires' disease in Philadelphia in 1976,[1] the search for and finding of outbreaks and cases and the identification of the organism have captured the interest of epidemiologists and microbiologists. Now, more than 2 years after the documented outbreak, the facts available on this fascinating disease are legion (pun intended) but incomplete.

Legionnaires' disease has almost certainly been present for some time. In the United States between 1976 and the end of 1978 there were approximately 10 confirmed outbreaks with about 500 cases; the ratio of males to females was 2.8:1 and the mortality was close to 14%. As well, there were 500 sporadic cases in 11 states; the ratio of males to females was 2.4:1 and the mortality 19%.[2]

During the same period 21 cases of Legionnaires' disease occurred in Canada. Of these, 18 serologically confirmed cases occurred in Ontario. All of the 18 were in adults; one woman died. No connection has been noted between 16 of the cases. The two exceptions were a husband and wife who took part in a London–Paris–Rhine Valley bus excursion in October 1978. Although the observations have yet to be confirmed and reported, they suggest a common source for the outbreak because many individuals on the bus tour were sick during the last part of the trip (J. Joshua: personal communication, 1979). One case of Legionnaires' disease has occurred in each of British Columbia, New Brunswick and Manitoba. In this issue of the Journal there are three reports of sporadic cases of Legionnaires' disease (see pages 1495, 1535 and 1537).

Cases have also been reported in Spain, Scotland and elsewhere in Europe during the past 2 years.[3]

Legionnaires' disease has an incubation period of 2 to 10 days. The disease is characterized by fever in 97% of cases, malaise in 89% and nonproductive cough in 80%. Other signs and symptoms include chills, dyspnea, myalgia, headache and chest pain. After pneumonitis ensues the chest roentgenogram shows patchy interstitial infiltrates or areas of consolidation. If effusion is present it is usually minimal. The emerging pattern of Legionnaires' disease includes not only respiratory symptoms, but also central nervous system and gastrointestinal manifestations and occasionally disseminated intravascular coagulation. Death is usually due to shock and respiratory failure.[1]

Currently the preferred therapeutic agent is erythromycin, which has been shown to have a minimal inhibitory concentration of 0.5 μg/ml. Erythromycin therapy should be maintained for 3 weeks.

Person-to-person spread of Legionnaires' disease has not been proven. However, in one instance a physician contracted Legionnaires' disease 7 days after examining a patient with the illness.[4] There are no proven animal sources or reservoirs.

As a result of investigations in Bloomington, Indiana; Memphis, Tennessee; and Atlanta, Georgia, the Legionnaires' disease bacterium has been recovered from water in two cooling towers, two evaporative condensers and one creek.[5] The organism has been shown to survive in both distilled and tap water for several months.

The Legionnaires' disease bacterium is a rugged, heat-stable, slow-growing, gram-negative short rod or long filamentous bacterium. The organism, while not yet taxonomically placed, has been given a name — *Legionella pneumophila*.[6] It is thought that the bacterium is transmitted as a secondary aerosol, often through water coolers and air-conditioning systems.[5]

Some 28 variations of the bacterium have been identified; however, 4 main serotypes associated with clinical disease have been named as follows:

- Knoxville, serotype 1: most outbreaks, including those in Philadelphia; Flint, Michigan; Burlington, Vermont; and Los Angeles (one of two episodes), have been caused by this strain.
- Togus, serotype 2: this strain was implicated in one case in Togus, Maine, one in Atlanta and the one in British Columbia.
- Bloomington 2, serotype 3: the outbreak in Bloomington, Indiana was caused by this strain.
- Los Angeles 1, serotype 4: this agent was responsible for one of the Los Angeles outbreaks.

The time-consuming indirect immunofluorescent antibody test is the most commonly used diagnostic procedure, and it is used in retrospective diagnosis. The antibody response tends to be slow; it takes 3 to 6 weeks for convalescent serum to show the diagnostically required fourfold increase in antibody titre to 1:128. A single titre of 1:256

is required for a presumptive serologic diagnosis.

The direct fluorescent antibody test is performed on tissue samples, usually lung biopsy specimens, but sometimes specimens from lung aspiration or transtracheal aspiration or bronchoscopy, and occasionally pleural fluid or sputum have given confirmatory results.

There is a need to develop a selective medium for the cultural recovery of *L. pneumophila*. To pass the bacterium through yolk sac and then transfer it into supportive media is time-consuming and expensive, and it results in an unsatisfactory delay. The development of an enzyme-liked immunosorbent assay, if possible, would be invaluable.

Priority must be given to the development of a method of rapid identification; perhaps the best avenue of approach might be to demonstrate direct fluorescent antibody on accessible specimens, such as blood, sputum or pharyngeal swabs. At present, indirect fluorescent antibody testing can be performed on paired samples of serum taken 3 weeks apart at the Laboratory Centre for Disease Control in Ottawa and by the laboratory services branch of the Ontario Ministry of Health.

There seems little doubt that Canada needs an *L. pneumophila* reference centre. The centre should be located at a laboratory that possesses the facilities to handle dangerous pathogens and the greatest professional expertise in this field. The centre should be able to make materials available to other laboratories for the performance of fluorescent antibody tests, and should be able to recover, isolate and identify the organism by culture methods.

A.J. CLAYTON, MB, CH B, DPH, FRCP[C]
Director-general
Laboratory Centre for Disease Control
Department of National Health
and Welfare
Ottawa, Ont.

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Diethylstilbestrol: risks of malignant disease and congenital malformations

In 1951 a prospective double-blind study was begun at the University of Chicago to evaluate the usefulness of diethylstilbestrol in the protection of pregnancy. The women involved, the controls and all the offspring are being carefully followed up. Preliminary long-term follow-up data, collected to the end of 1977, have been reviewed by a task force of the Department of National Health and Welfare's special advisory committee on reproductive physiology.

The Chicago study[1] and others[2,3] have demonstrated that the female offspring of women given diethylstilbestrol during pregnancy are at an increased risk for a variety of benign abnormalities of the genital tract. In addition, the very infrequent occurrence of carcinoma of the vagina or cervix in such individuals is well documented.[4] It is now also evident that prenatal exposure of males to diethylstilbestrol is associated with a low frequency of various detectable anatomic and functional changes in the reproductive tract.[1,2,5,6] The abnormalities observed include epididymal cysts, hypoplastic testes, induration of the testicular capsule, and some impairment of spermatogenesis, sperm maturation and accessory gland secretion; malignant lesions have not been reported.

The women who had received diethylstilbestrol during pregnancy are also being closely observed. Preliminary data have suggested that there may be an increased risk of breast cancer in these women. However, the data are inconclusive and the difference in the incidence of breast cancer in women exposed to diethylstilbestrol and those not exposed is not significant. Nevertheless, it seems prudent to advise all women who have been exposed to diethylstilbestrol or other estrogenic drugs during pregnancy to undergo regular breast and gynecologic examinations.

The advisory committee believes that the use of diethylstilbestrol and other estrogenic drugs during pregnancy for the treatment of threatened or habitual abortion is hazardous to the fetus. Congenital and developmental anomalies of the reproductive tract in female and male offspring of women treated during pregnancy with diethylstilbestrol or other estrogens were first recognized in the early 1970s. Since then all estrogenic drugs have been labelled as contraindicated during pregnancy. The committee strongly recommends that the future clinical use of diethylstilbestrol be limited to the palliative treatment of patients with estrogen-responsive metastatic breast carcinoma or advanced carcinoma of the prostate.

The health protection branch of the Department of National Health and Welfare concurs with the views of the committee and has asked the manufacturers of diethylstilbestrol to update the directions for its use and