Lassa fever, Marburg and Ebola virus diseases and other exotic diseases: Is there a risk to Canada?

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There are seven exotic diseases of concern; three of these, the most unpredictable and least understood, are Lassa fever, Marburg virus disease and Ebola virus disease. In this article the epidemiologic aspects of these diseases are discussed, with particular emphasis on exportation from their indigenous areas in Africa and on the occurrence of secondary cases.

Any of these conditions could be brought into Canada either by aeromedical evacuation or inadvertently. Between 1972 and 1978 there were seven occasions when Canada could have been involved with handling cases of Lassa fever.

The Government of Canada has purchased several containment bed and transit isolators. These units, with filtered air under negative pressure, accommodate infectious patients being transported and cared for without contaminating medical attendants or the environment.

Il existe sept maladies exotiques sérieuses; parmi celles-ci, les trois qui sont les plus imprévisibles et les peu comprises sont la fièvre de Lassa, la maladie à virus de Marburg et la maladie à virus Ebola. Dans cet article les aspects épidémiologiques sont discutés, surtout en ce qui concerne leur dissémination à partir des lieux indigènes en Afrique et l'incidence des cas de contagion.

N'importe laquelle de ces maladies est susceptible d'être introduite au Canada soit lors d'évacuation aéromédicale ou par inadvertance. Entre 1972 et 1978 le Canada aurait pu être amené à traiter des cas de fièvre de Lassa à sept reprises.

Le Gouvernement du Canada a acheté plusieurs lits et postes mobiles d'isolement. Ces unités, qui possèdent l'air filtré à pression négative, hébergent les patients infectieuses qui sont transportés et soignés sans contaminant l'équipe médicale ou l'environnement.

Exotic diseases can be described as highly virulent and transmissible diseases that are not indigenous at this time in Canada. The Working Party on Coordinated Response to National Communicable Disease Emergencies, constituted under the authority of the health protection branch of Health and Welfare Canada, has listed the following exotic diseases as those about which concern of importation has been expressed: Lassa fever; Marburg virus disease; African hemorrhagic fever or Ebola virus disease; Argentinian hemorrhagic fever or Junin virus fever; Bolivian hemorrhagic fever or Machupo virus fever; smallpox; and pneumonic plague.[1]

The concern expressed in the title of this paper is directed to Lassa fever, Marburg virus disease and Ebola virus disease. The South American hemorrhagic fevers have not been encountered outside their indigenous areas, except for laboratory-acquired cases. Naturally acquired smallpox has been almost totally eradicated throughout the world. The laboratory acquired and subsequent secondary cases of smallpox in Birmingham, England during the summer of 1978 are of concern.[2,3] Pneumonic plague remains a threat, but it appears that the natural history of plague is such that today the bubonic form predominates, largely in the sylvatic form.

It is thus appropriate to look at the first three of the exotic diseases listed, and from an epidemiologic point of view examine them with a view to possible exportation from their indigenous areas.

These diseases are not only highly virulent and communicable but also at times highly transmissible. It is this unpredictability and the as yet little understood transmissibility that present the problem of importation into the Western world.

Lassa fever

Lassa fever was first recognized by Frame and colleagues[4] in 1962, when three cases occurred in the small village of Lassa in northeastern Nigeria. In early 1970 a second reported outbreak occurred at Jos, in north-central Nigeria.[5] From Jos a 52-year-old missionary nurse was aeromedically evacuated via Lagos to New York City in the first-class section of a commercial Boeing 707 aircraft. It has been shown that the ventilation patterns within this type of aircraft are such that the ideal place to carry a patient with a highly infectious disease is at the rear of the aircraft;[6] however, fortuitously, no fellow passengers became infected. During the period of laboratory examination of specimens in the United States two scientists contracted Lassa fever and one died, but the nurse survived. The virus was isolated and identified at that time.[7]

Over the next 6 years there were five further importations of this disease from West Africa.

In 1972 a 25-year-old nurse fell sick in Panguma, Sierra Leone and made her own arrangements to travel to London, England.[8] The diagnosis was not made until after she had recovered; therefore, no contact surveillance was applied to other passengers. It appears that there were no secondary cases.

Two more years passed before

Featured on the cover of this issue of the Journal is a Department of National Defence photograph of a containment bed isolator (Vickers) whose filtered air is under negative pressure. Such units are used in the care of persons with exotic diseases who must be kept in complete microbiologic isolation.

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the next international event. In March 1974 a 33-year-old West German physician contracted Lassa fever in Onitsha, Nigeria.[9] He was flown to Hamburg, West Germany in a "dedicated" aeromedical evacuation, which means that the mission or flight was devoted to that purpose, and, therefore, no other passengers were carried. The strict isolation techniques that were employed on this flight have been described by Renemann.[10] The patient survived and there were no secondary cases outside Nigeria. This was the first occasion on which dedicated aeromedical evacuation was used.

The next importation occurred in January 1975, when a British physician arranged his own flight from Kano, in northern Nigeria, to London, England via Brussels.[11] On arrival in London he was acutely ill; he was admitted to hospital immediately, but died the next day. Although he was in contact with some 200 people, no secondary cases occurred.

In March 1976 the scene shifted back to Sierra Leone. A 42-year-old Peace Corps worker had been ill for several weeks in Mobai, Sierra Leone.[12] She was advised to return home to the United States, and arrived in Washington after travelling on two aircraft — a Boeing 707 from Sierra Leone to London, England, then a Boeing 747 to Washington. A positive diagnosis was made when Lassa virus was isolated from her urine. She recovered, and none of the 300 contacts contracted the disease.

The sixth and last importation to date occurred in July 1976, when a 33-year-old British engineer became sick while working in Nigeria.[13] He returned home to England and was admitted to hospital. After his discharge Lassa virus was recovered from a urine specimen; he was therefore readmitted to hospital and a positive diagnosis was made.

The interesting feature of the exported disease is that, apart from two laboratory-acquired cases, no secondary person-to-person transfer occurred outside West Africa, where, contrastingly, the disease shows a great deal of unpredictability in terms of its transmissibility. The virus rarely spreads beyond three generations in nosocomial outbreaks. Transmission occurs predominantly through parenteral means but, because the virus has been recovered from the pharynx, person-to-person airborne spread is likely. The mortality in hospitalized cases is close to 50%; patients tend to die around the 12th day.

Marburg virus disease

Marburg virus disease is named for the small town in West Germany where the disease was first reported and identified, in the summer of 1967.[14] A consignment of Vervet (green monkeys) was shipped from Uganda to three laboratories in Belgrade, Frankfurt and Marburg. Thirty-one workers in these laboratories or close associates were infected, and seven died. In contradistinction to Lassa fever, Marburg virus disease was transmitted secondarily to six individuals — five medical personnel and one person who acquired the disease through sexual contact 83 days after the onset of illness in the index case. The mortality in this outbreak was 23%.

Nothing more was seen or heard of Marburg virus disease until 1975, when a 20-year-old Australian hitchhiker fell sick in Rhodesia.[15] He was admitted to hospital in Johannesburg, where he died. His travelling companion and an attending nurse at the hospital were the only persons to acquire the disease secondarily, and both survived.

Marburg virus disease has not been recognized or encountered since then, and these two outbreaks represent the only recorded episodes of the disease. The assumption can be made that cases could occur at any time. Thus, as with Lassa fever, the unpredictability of Marburg virus disease remains the chief concern.

Ebola virus disease

African hemorrhagic fever, or Ebola virus disease, first emerged in the southern Sudan in June 1976. Between then and November 1976 there were two parallel outbreaks in southern Sudan and northern Zaire.[16,17] The disease is named after a small river in northern Zaire.

In the southern Sudan there were 299 cases during the 4-month period, with 150 deaths — a case fatality rate of 50%. However, the disease in Zaire was even more serious in terms of virulence and transmissibility. There were 237 cases, with 211 deaths, including cases imported from northern Zaire into Kinshasa, where two generations of illness occurred. The mortality was thus 89%.[16] Ebola virus disease, therefore, is probably the most fatal infectious disease, apart from rabies, that has been reported to date.

At the Microbiological Research Establishment at Porton Down, England, a virologist accidently pricked his finger while working with virus cultures.[18] Five days later the classical symptoms of Ebola virus disease developed. He was nursed in a Trexler containment bed isolator during his illness.[19] He made a good recovery, but virus was recovered from his seminal fluid up to 3 months after clinical recovery.

Once again, it is largely the unknown features and unpredictability of this disease that give concern about the likelihood of future exportation from Africa.

Canadian experience with exotic diseases

There are three eventualities that could lead to importation and subsequent recognition of these diseases in Canada: (a) a patient could arrive by means of dedicated aeromedical evacuation; (b) a person could become sick en route to Canada or be discovered to be ill at the port of entry; or (c) a person could fall sick after arriving in Canada. In the third category the illness might be discovered under several circumstances — for example, in a community hospital or in a private home. The implications of possible secondary spread are enormous, for the individual could have been shedding organisms into the ecosystem for sev-

eral days while the disease was in the incubation stage.

Canada has had complete or partial involvement in such circumstances on seven occasions during the past 5 years.

In September 1972 a 20-year-old laboratory worker at Panguma, Sierra Leone became ill and requested of her parent organization — Canadian University Services Overseas (CUSO) — that she be permitted to return to Canada. The minister of external affairs acceded to this request and asked the minister of national defence if an aircraft could be made available to transport her back to Canada; however, her condition rapidly improved and the request was rescinded.

In March 1974 an almost identical request was received from CUSO in Nigeria. A wife of a Canadian teacher fell ill during the Onitsha outbreak, when the West German physician was evacuated to Hamburg.[9] The Canadian Forces were once again asked to undertake a medical evacuation from Nigeria to Canada. On this occasion the aircraft was within 2 to 3 hours of leaving when the request was withdrawn.

The next Canadian involvement was in March 1976. There were three Canadians travelling from Sierra Leone to London on the commercial Boeing 707 that carried the ill United States Peace Corps worker described earlier.[12] These travellers were later located in Edmonton and Ottawa, and the one in Ottawa was found to be sick in a hotel; however, after appropriate measures were taken it was shown that he did not have Lassa fever.

The fourth event was in August 1976, when a 50-year-old woman who had been travelling in Europe fell ill at Toronto International Airport. She was admitted to hospital, and 7 days after admission it was found that she had antibodies to Lassa fever virus.[20] The case remains an enigma, for the woman had never been to West Africa, as far as is known, had had no contact with any person with proven Lassa fever, and did not have more than a vague connection with persons from Nigeria; in addition, Lassa fever virus was never recovered from her. The titre of IgM immunoglobulins against Lassa virus was sufficiently high for it to be unlikely that cross-reaction with other arenaviruses could be implicated. It will probably never be shown whether this woman had Lassa fever.

The fifth Canadian experience was in June 1977, when a 6-year-old boy travelling with his missionary parents on a chartered aircraft from Nigeria via Canada to the United States was found to be sick on the aircraft at Toronto International Airport. He was taken to a medical holding area at the airport. Later that day he and his family — father, mother and brother — were transported in a Canadian Forces Hercules aircraft from Toronto to Ottawa. The patient was placed in a containment aircraft transit isolator, which supplies its own filtered, negatively pressurized air in such a way that patients can be transported and cared for in a microbiologic containment mode. The patient was placed in a containment bed isolator at the National Defence Medical Centre in Ottawa, where he remained for 4 days.

In May 1978 a woman was travelling from the Ivory Coast to Montreal via Brussels. Quarantine officials were notified prior to her arrival in Canada that she was suspected of having Lassa fever. For the first time the provisions of the Canadian Contingency Plan were put into effect.[1] A Department of National Defence standby team was alerted for transportation of the patient from Montreal to Ottawa if considered necessary. After examination at Mirabel Airport the patient was considered not to have an exotic disease.

In July 1978 the seventh and final episode occurred. A woman had previously returned to Toronto from Nigeria 5 days before being examined at the tropical medicine unit of Toronto General Hospital. Her symptoms were suggestive of early Lassa fever, and she was placed in residential quarantine while a definitive diagnosis was made. Once again the Contingency Plan was evoked, with arrangements for dedicated aeromedical evacuation to Ottawa if requested by provincial authorities. However, a group B arbovirus (flavivirus) disease was diagnosed serologically.

Proposed methods of handling cases of exotic diseases

In March 1974, when the second request for aeromedical evacuation was made, it was realized that there were no adequate isolation facilities in Canada — facilities where patients with these highly transmissible diseases could be cared for while the safety of medical attendants could be assured and, just as important, escape of virulent organisms into the environment could be prevented. It is not known whether insects infesting small mammals can harbour these organisms and thereby become a reservoir, so that these diseases can become established in Canada in a manner similar to that in which rabies became epizootic.

The Department of National Defence made a commitment to the Government of Canada that any patient with an exotic disease could be admitted to the National Defence Medical Centre, provided he or she was not already an inpatient at another Canadian hospital. This provision was made because the facilities for isolation at the National Defence Medical Centre were no better than those at any other hospital in Canada. Moreover, interhospital transfer would do little more than double the number of persons already exposed.

The federal government constituted in the fall of 1975 an Isolation Facilities Working Group (of which I was a member) composed of federal and provincial representatives. After nearly 2 years of deliberations and liaison visits to the United States and Europe the group recommended to the minister of national health and welfare that Canada needs a national reception centre of six-bed capacity at which patients suspected of harbouring infectious or contagious diseases may be isolated, lifesaving medical treatment may be offered, and protection may be given against the spread to others and to the environment, and that Canada should con-

comitantly establish a class 4 biohazards laboratory so that essential investigations may be safely conducted to determine the cause and to monitor the duration of disease activity. At present, only the Center for Disease Control in Atlanta, Georgia and the Microbiological Research Establishment at Porton Down, England are capable of isolating viruses from patients with exotic diseases.

Interim measures for isolating patients with exotic diseases

During the deliberations of the Isolation Facilities Working Group it was realized that the risk of importation of an exotic disease during the Olympic Games in July 1976 was higher than usual. However, during a visit to England, members of a subcommittee of this group became acquainted with the Trexler isolator; accordingly, three containment bed isolators were purchased by the federal government and were received in June 1976. Two were immediately erected at the National Defence Medical Centre and one was placed in storage and then 4 months later sent to Zaire with a Canadian Forces technician to be used for the care of members of the World Health Organization's investigation team studying and controlling the outbreak of Ebola virus disease referred to earlier.[15]

The containment bed isolator,[19] manufactured by Vickers Ltd. Medical Engineering, Basingstoke, England, consists of two rectangular envelopes constructed of transparent polyvinylchloride plastic (Fig. 1).

The larger envelope (bed section) which is 2.4 m long, 1.8 m wide and 2.0 m high, is suspended from a frame and placed over an intensive care bed in such a manner that the patient is in complete microbiologic isolation. The patient is accessible to medical and nursing care by means of half-suits, which are evaginations of the side walls of the envelope that are donned by medical personnel. The air supply within the unit is maintained by blower motors that provide 15 changes of appropriately filtered air per hour and negative pressure compared with the outside atmosphere. (The apparatus can also be used in the care of persons who are immunologically compromised, but in this case the air is under positive pressure.)

The smaller envelope is a supply section into which items such as food or medication can be introduced and prepared for the patient. Contaminated articles are removed without breaking the integrity of the envelope.

Soon after these isolators were acquired it was realized that there was a need for similar types of apparatus by which patients could be moved and transported. Accordingly, two further generations of isolators have been developed: a containment stretcher isolator, which can be taken to a patient's bedside, where the patient is lifted into and carried on the stretcher within a microbiologically safe environment; and a larger portable isolator, known as the containment aircraft transit isolator, with which the stretcher isolator can dock (Figs. 2 and 3). The containment aircraft transit isolator was used for the first time in North America and the second time ever in June 1977 to transport from Toronto to Ottawa the 6-year-old boy with suspected Lassa fever described earlier.

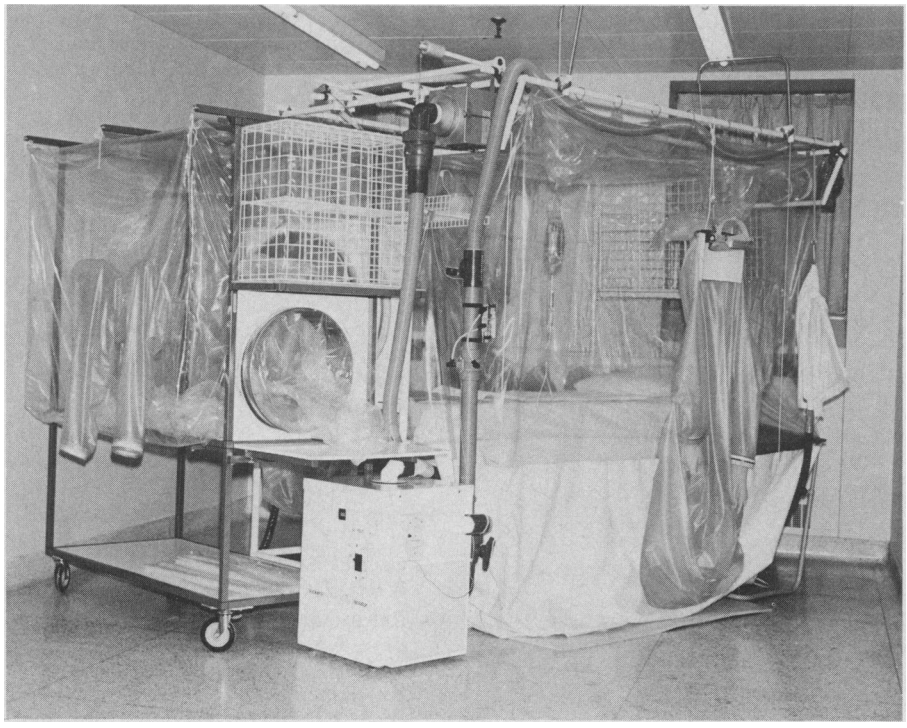

FIG. 1—Containment bed isolator, incorporating bed and supply sections (Vickers Ltd. Medical Engineering, Basingstoke, England).

Discussion and conclusions

The title of this paper asked, in part, the question Is there a risk to Canada with respect to the importation of exotic diseases? The paper has attempted to show what the propensity for spread can be and what the experience with respect to importation in the world generally and in Canada specifically has been. It is clear, with one possible exception, that none of these diseases has been encountered in this country recently. In fact, the last case of smallpox in Canada was in 1962. However, it is apparent, I believe, that the risk of importation of an exotic disease is high. Indeed, with increasing travel to developing and tropical areas, such importation into Canada seems almost inevitable. This is underlined by the existence of two confirmed cases in the United States and three in Britain. The other factor that must be considered is that Canadians working overseas have the right to ask to be returned home if they are sick. Whether such persons should be permitted to return to Canada is a moral question and is beyond the scope of this paper.

Further, so-called Lassa fever alerts have occurred one or two times a year. It can confidently be expected that these alerts will become more frequent. As long as a presumptive diagnosis has been made, containment precautions must be instituted until it is proven that the condition is other than one of the exotic diseases. Finally, the laboratory acquired cases of smallpox in England in 1978, the Ebola virus disease in England in 1976 and the two cases of Lassa fever in the United States in 1970 indicate that this type of infection must also be uppermost in one's mind when planning for the handling of cases of exotic disease.

At present, the cause, means of transmission, and degree of transmissibility and virulence of the exotic diseases are only partly understood; what is clear, however, is that they are unpredictable. Until they are fully understood in all facets, it seems only reasonable that the precautions that have been or are being taken should be continued.

The answer to the question in the title is, therefore, a clear Yes, and planning and preparations must be effected accordingly.

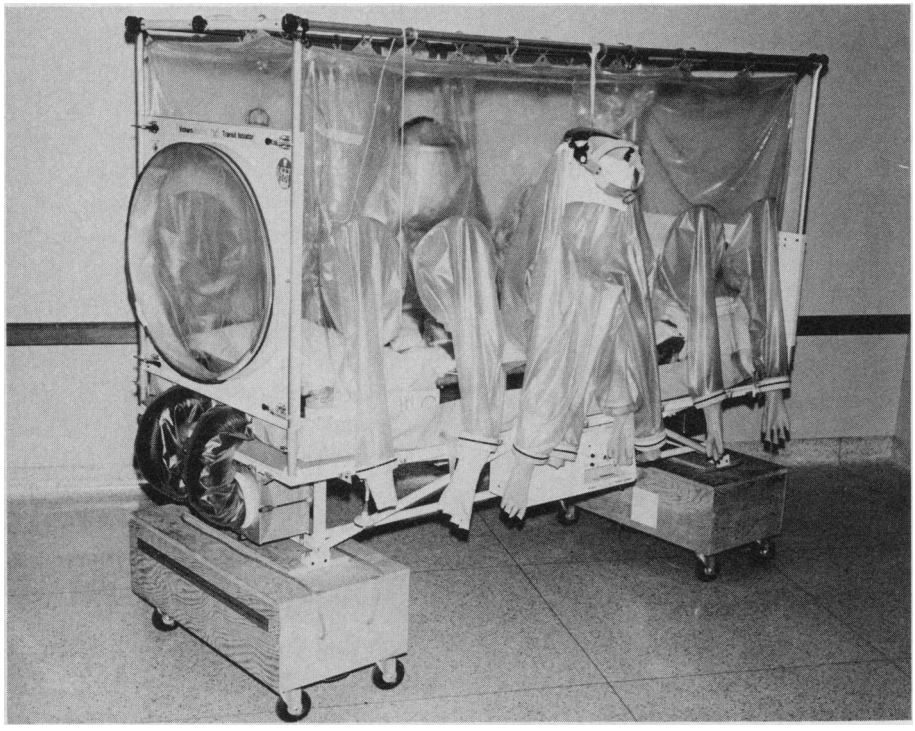

FIG. 2—Containment aircraft transit isolator (Vickers).

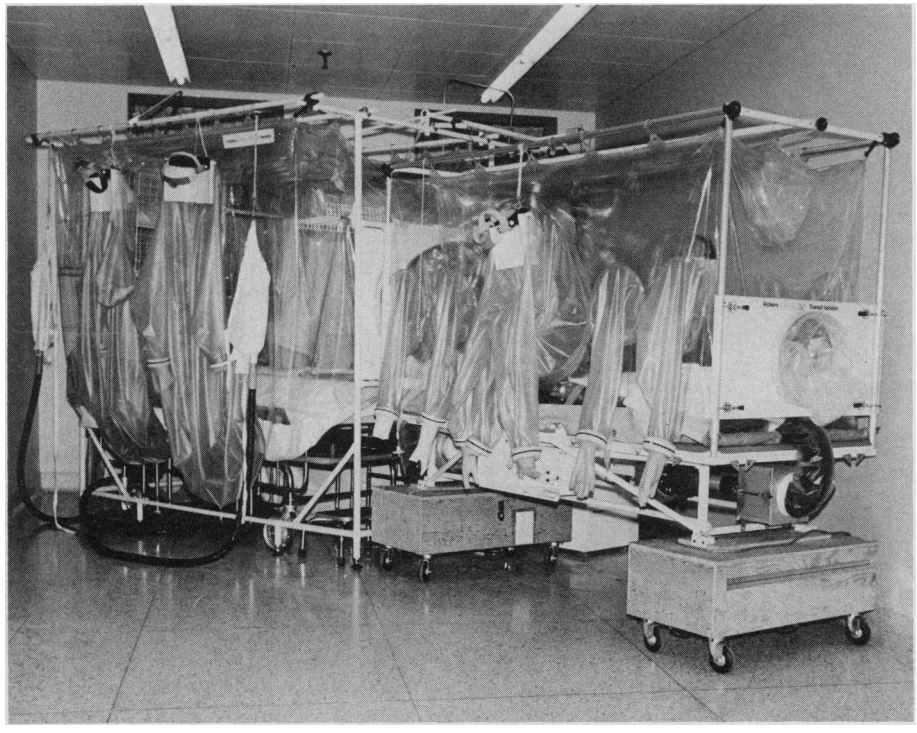

FIG. 3—Containment bed and containment aircraft transit isolators in docked position.

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Meningococcal meningitis in children

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Forty-four cases of meningococcal meningitis in children at one hospital between 1971 and 1975 inclusive were studied to document the course and complications of this disease in children in the current therapeutic era. The mortality was 5%. Of the 41 survivors 76% were healthy 1 to 5 years after the episode of meningitis. Permanent severe sequelae (facial palsy, optic atrophy and ptosis) were seen in three (7%) of the survivors, and mild hearing loss, hyperactivity and nervousness were noted in seven (17%). Electroencephalography was not useful in determining management or prognosis. Both the mortality and the frequency of early and late complications among the survivors were lower than those reported from earlier studies.

Quarante-quatre cas de méningite à méningocoque chez des enfants dans un hôpital entre 1971 et 1975 inclusivement ont été étudiés pour documenter l'évolution et les complications de cette maladie chez des enfants dans l'ère thérapeutique actuelle. La mortalité était de 5%. Parmi les 41 survivants 76% étaient en bonne santé 1 à 5 ans après l'épisode de méningite. Des séquelles graves permanentes (paralysie faciale, atrophie optique et ptosis) ont été observées chez trois (7%) des survivants, et une légère hypoacousie, une hyperactivité et une nervosité ont été notées chez sept (17%). L'examen électroencéphalographique n'a pas fourni d'éléments d'intérêt thérapeutique ou pronostique. La mortalité et la fréquence des complications précoces et tardives chez les survivants ont été plus faibles que celles rapportées dans les études précédentes.

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Haggerty and Ziai[1] and Swartz and Dodge[2] reported mortality rates for meningococcal meningitis in children of 18% and 13% in 1964 and 1965 respectively. Wehrle and colleagues[3] reported an average mortality of 8.4% (range 3.3% to 14.1%) for the years 1961 through 1966. A more recent survey of bacterial meningitis in children in England and Wales documented a mortality of approximately 22% for cases reported in the years 1970 through 1973, but more detailed examination of the records of 265 of the patients from an area in London disclosed a mortality of 11% in this group.[4] Unfortunately data relating to early and late morbidity and clinical and laboratory features of meningococcal meningitis were not provided in this report — nor have these features been described in the modern therapeutic era.

We have followed up children with meningococcal meningitis admitted to the Montreal Children's Hospital between 1971 and 1975 inclusive to document the early and late complications of this disease and to estimate the current mortality. The results of this study indicate a low mortality (5%) and a reduction in the frequency of some complications, compared with earlier data.[1-4]

Methods

The clinical and laboratory features of children hospitalized at the Montreal Children's Hospital with meningococcal meningitis (those in whom *Neisseria meningitidis* was cultured from cerebrospinal fluid [CSF]) during the years 1971 through 1975 were analysed.

Of the 41 survivors 36 were examined at 2 weeks, 2 months, 6 months and 1 year after discharge from hospital. Information about the remainder was obtained from the charts, their physicians and the answers to a telephone questionnaire. Each visit included interval history-taking and physical, neurologic and developmental examination. Audiograms and electroencephalograms (EEGs) were obtained within the first 3 months after the illness and were repeated when abnormal.

Results

There were 44 cases of meningococcal meningitis in 43 children admitted to our hospital between 1971 and 1975. Twenty-six (60%) of the children were male, and the average age was 2½ years (range 2 months to 16½ years). Two patients died. One, a 2-year-old boy, presented with convulsions and hyperglycemia after 6 hours of fever and vomiting. Disseminated intravascular coagulation developed rapidly, and he died 39 hours after admission; histopathologic findings indicated Waterhouse-Friderichsen syndrome. The other was a 7-year-old girl who presented with a 3-hour history of vomiting, fever and delirium, and died in shock 8 hours after admission.