Laboratory and Clinical Features of Influenza
A₂ 1971-72 in Montreal

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Virologic, serologic and clinical records at two Montreal hospitals revealed 19 adults and 27 children with influenza A₂ (Hong Kong variant) infections during the winter months of 1971/72. Serious disease and two deaths were encountered in 14 (51 percent) children with underlying disease and 15 (55 percent) below three years of age. Six (22 percent) children had pneumonia, nine (33 percent) gastrointestinal symptoms, two conjunctivitis, and two meningitis. Of seven (37 percent) adult patients with complications, six (32 percent) had pneumonia, two pancreatitis, and five (26 percent) underlying disease. Two adult patients with no previous history of illness had a fulminant course and died within 48 hours of admission. Influenza continues to be associated with severe illness in a few patients especially, but not exclusively, in high risk individuals.

Reports in recent years have emphasized the diverse manifestations and clinical presentations of influenza infections. This review describes some of the serious influenza A₂ infections seen during the 1971-72 outbreak in Montreal. Comparisons to previous epidemics and differences in clinical presentation between adults and children are featured. Included are virologic, serologic and clinical data of 19 adults and 27 children with influenza A₂/Hong Kong variant infections from the Montreal Children's Hospital and the Royal Victoria Hospital.

METHODS

Virus isolation techniques

Specimens were diluted in 2 ml transport medium (50 percent tryptose phosphate broth in Hank's balanced salt solution with 1 percent inactivated fetal agama calf serum) and treated with penicillin, streptomycin and amphotericin B (Fungizone). They were inoculated into two tubes each of primary rhesus monkey kidney, Hep₂ (carcinoma of the nasopharynx) and Wistar 38 (human embryonic lung) cells. Specimens that were negative in tissue culture were tested in ten-day-old chick embryos by the amniotic route. Cells were maintained in a medium consisting of 49 percent medium 199, 49 percent Eagle's minimum essential medium and 2 percent inactivated agama calf serum. Rhesus monkey kidney cells were rotated on roller drums and the other cells maintained stationary at 35°C for at least two weeks. Cells were checked daily for cytopathic effect and rhesus monkey kidney cells were tested for hemadsorption after three to five days of incubation.

Virus identification

Virus identification was done by hemadsorption-inhibition and hemagglutination-inhibition tests using specific rabbit antiserum to influenza A₂/Hong Kong/68 (Flow Laboratories, lot No 825006) titered at 1:160, heat inactivated, treated with kaolin and absorbed with guinea pig red blood cells.

Serologic diagnosis

Serologic diagnosis was based on demonstration of a four-fold or greater increase in antibody titer between acute and convalescent sera measured by complement-fixation with use of soluble antigen using the microtiter technique.

Clinical Manifestations

The clinical records of 19 adults (>18 years of age) from the Royal Victoria Hospital and 27 children from the Montreal Children's Hospital with documented influenza A₂ infection were analyzed retrospectively. Since the studies were not planned in a prospective manner, criteria for clinical assessment of severity of disease and the necessity for hospitalization were not uniform. Signs, symptoms and laboratory investigations were analyzed.

RESULTS

Isolation and identification of the virus

Influenza virus A₂/Hong Kong/68 was isolated from 45 patients—18 adults and 27 children. One of the isolates was referred to the WHO International Influenza Center for the Americas, Center for Disease Control in Atlanta, Georgia. It was confirmed as being A (N₂) strain by hemagglutination-inhibition using chicken antisera prepared against purified A/AICHI/2/68 (N₂) hemagglutinin.

Rhesus monkey kidney proved to be satisfactory for virus isolation. However, two isolations were made in chick embryo from specimens that were negative in rhesus monkey kidney. A combination of both methods of isolation would give the largest number of isolations. Cytopathic effect (CPE) in
rhesus monkey kidney cells was present in 5 of the 18 adult isolates and in 22 of the 27 isolates from children. In some cases, CPE appeared as soon as 48 to 72 hours after inoculation. In one instance, slight CPE and hemadsorption were observed after 12 hours of incubation. Early CPE was useful in providing rapid diagnoses once the outbreak was established. Hemadsorption was performed as soon as CPE was diagnosed and the preliminary report sent out.

Six original specimens from the patients later shown to be positive by tissue culture were studied by electron microscopy; no viruses were visualized. Nevertheless, the electron microscope was useful in establishing the virus group early in the outbreak when isolates cross-reacted with paramyxoviruses in inhibition tests. The tissue culture fluids from these isolates were passaged to eggs and the myxovirus particles were seen under the electron microscope in the amniotic fluid.

Serologic results

Paired sera were received from five adults and six children who had positive isolates. Four of these in each group showed a four-fold or greater rise in antibody titer by complement-fixation. A four-fold or greater rise in antibody titer by complement-fixation without virus isolation was observed in six adult patients hospitalized with diagnosis of pneumonia and influenza. Specimens for virus isolation were obtained from only one patient of this group and gave negative results.

Clinical manifestations

There was only one complication (pneumonia) among 13 nonhospitalized adults; this patient was a 66-year-old woman with hypertension and angina. All of five hospitalized adults with positive virus isolations developed serious complications (Table 1); one patient died. This was a woman, 59 years of age, who developed acute bilateral pneumonia, congestive heart failure, acute renal failure, pancreatitis and disseminated intravascular coagulation; she died within 48 hours of admission to hospital. The possibility of pancreatic involvement was considered in 11 other adult patients. Their sera were tested for amylase levels but were within normal limits. All except the patient who died had underlying illnesses including chronic lung disease, chronic heart failure and diabetes mellitus.

Two important factors influenced the clinical illness among children with influenza: (a) the age of patients (b) the underlying disease. Sixteen patients (59 percent) who developed serious disease were under three years of age. The presenting signs and symptoms of children with influenza are illustrated in Figure 1. Twenty-one (77.7 percent) presented with upper and lower respiratory symptoms (Table 2), eight (29.6 percent) developed pneumonia and three (11 percent) croup. Six (22.2 percent) patients presented with gastrointestinal symptoms such as anorexia, vomiting and diarrhea associated with respiratory symptoms. Convulsions were observed in three patients (11 percent). One of these patients had aseptic meningitis confirmed by examination of the cerebrospinal fluid (CSF). Influenza virus was isolated from the nasopharynx but not the CSF. In all cases, convulsions were accompanied by high fever. One patient had leg weakness and ataxia as well, but the CSF examination was normal.

Eleven (40.7 percent) children with underlying disease had serious illness (Table 2). Twenty-two

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying Disease</th>
<th>Course and Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>18</td>
<td>M</td>
<td>Chronic obstructive lung disease, chronic heart failure</td>
<td>Complicated by pulmonary embolism</td>
</tr>
<tr>
<td>15</td>
<td>73</td>
<td>F</td>
<td>Diabetes mellitus, urinary tract infection</td>
<td>Complicated by pneumococcal pneumonia</td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>F</td>
<td>Diabetes mellitus, hypertension</td>
<td>Influenza acquired in hospital; had been admitted for dyshidrosis. Complicated by Hemophilus Influenzae pneumonia.</td>
</tr>
<tr>
<td>17</td>
<td>70</td>
<td>M</td>
<td>Chronic bronchitis</td>
<td>Admitted for hip fracture. Had broncho-pneumonia on admission, complicated by necrotizing pneumonia. Lung abscess—aspergillosis.</td>
</tr>
<tr>
<td>18</td>
<td>59</td>
<td>F</td>
<td>None</td>
<td>Acute bilateral alveolar pneumonia Congestive heart failure Acute renal failure Pancreatitis Bleeding diathesis Disseminated intravascular coagulation Death within 48 hours after admission to hospital.</td>
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(81 percent) children required hospitalization; of those, 15 (68 percent) were under three years of age. The older children had underlying diseases such as ataxia telangiectasia, chronic lung disease and malabsorption. Two children died. One was a baby five months old with psychomotor retardation of unknown cause who developed pneumonia. This patient had a lung aspiration before death from which the virus was isolated. The second patient had been followed throughout childhood with ataxia telangiectasia, chronic respiratory failure and pulmonary hypertension, immunoglobulin A (IgA) deficiency and cachexia. He developed pneumonia and died two months following influenza virus isolation from throat swab and tracheal aspiration.

**DISCUSSION**

The majority of children presented with respiratory symptoms. As in other outbreaks, bacterial pneumonia accompanying influenza pneumonia or complicating the later stages of influenza infection did not play as significant a role in this outbreak especially in children.

A relatively new feature was the appearance of croup in this outbreak. Croup was probably due to subglottic edema and was indistinguishable clinically from parainfluenza-associated croup. In general, involvement was mild and no tracheostomies were required. In this respect, our experience differs from the epidemic which occurred in Texas during January and February 1972 when eight cases of influenza A2 virus resulted in croup requiring tracheostomy.1

Various neurologic complications of influenza A2 virus infection or vaccination in previous outbreaks have been described.10-14 Three groups have been defined: encephalopathy, myelopathy and polyneuropathy. The most common type was polyneuropathy of motor and sensory type during recovery from influenza. These patients presented with numbness, weakness of proximal muscles of the arms and legs, absence of tendon jerks, flaccid paralysis and tenderness. The CSF revealed minimal pleocytosis with some increase in protein. Steroid therapy seemed to hasten recovery. A recent report from England15 described a high incidence of convulsions (50 percent) among children with influenza admitted to hospital (this represented 40 percent of children with influenza in their series). However, none of the patients had clinical evidence of encephalitis and the cerebrospinal fluid of the five investigated were normal. Hence, it is doubtful that this figure represents a real increase in neurologic complications of influenza outbreak 1971-72. In our group of patients, only three presented with convulsions. A diagnosis of aseptic meningitis was made in one of them and documented by lumbar puncture. However, the influenza virus was isolated only from the nasopharynx. In two other cases, the convulsions occurred during febrile illness two months and six weeks respectively prior to virus isolation. It has recently been indicated16 that virus excretion may be prolonged well beyond the acute stage of illness in naturally occurring influenza infections.

Severe myositis among 26 children was described in previous influenza outbreaks.17,18 It occurred in the recovery phase of respiratory influenza and was so severe that affected children refused to walk. It lasted an average of one to five days and in one patient, up to seven weeks. In our studies this was a rare presentation and not in severe form.

In both the adult and the children's groups, the presence of underlying disease was an important factor. Conditions predisposing to a more severe course of infection included chronic respiratory disease, congenital heart disease and/or congestive heart failure, immunologic deficiencies, diabetes mellitus and other metabolic disorders. Influenza did not appear to increase the incidence of ketoadsosis among children or adults with diabetes in our series.19,20 Certain laboratory features of this epidemic deserve emphasis. Early diagnosis was accomplished by lung aspiration21 and the rapid appearance of CPE in primary rhesus monkey kidney cells. Electron microscopy was helpful in differ-

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**Table 2—List of Underlying Diseases of Children with Influenza A₂ Virus Infection Seen at the Montreal Children's Hospital, Winter—1971-72**

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>1 Psychomotor retardation of unknown etiology</td>
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<tr>
<td>2 Chronic lung disease</td>
</tr>
<tr>
<td>3 Ataxia telangiectasia with chronic respiratory failure, pulmonary hypertension, IgA deficiency cachexia</td>
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<tr>
<td>4 Adrenogenital syndrome</td>
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<td>5 IgA deficiency with malabsorption</td>
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<td>6 Anemia</td>
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<tr>
<td>7 Mongolism with stage 3 rickets</td>
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<tr>
<td>8 Congenital heart disease</td>
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</tbody>
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entiating myxo from paramyxo viruses in egg culture material. The rapid, careful handling of clinical samples of nasopharyngeal and tracheal secretions, sputum and lung aspiration material with careful attention to CPE and prompt testing for hemadsorption were essential steps in early presumptive virologic diagnosis.

REFERENCES
12 Wells CEC: Neurological complications of so-called "Influenza"—a winter study in South-east Wales. Br Med J 1:369, 1971
17 Hoefnagel D: Severe myositis during recovery from influenza. Lancet 2:720, 1970

Tapestry of Lasting Fame

The year of 1662 marks an outstanding date in the history of French decorative art, for it witnessed the creation of the Gobelins which for more than three centuries was to produce those splendid tapestries that have made the name "Gobelins" famous. On June 6, 1662, Louis XIV bought from Sieur Lelu the hôtel of the Gobelin family for the sum of 40,775 livres. This old Parisian family, which gave its name to the royal factory, was descended from a certain Philibert Gobelin who died before 1510 and who during his lifetime was a merchant dyer of scarlet fabrics. As early as the seventeenth century the tapestries woven at the Gobelins became famous and even today there is a tendency to use the word "Gobelins" for any tapestry with little concern for the date of execution and the workshop in which it was made. Here at the Gobelins the King's Controller General of Finances, Colbert, concentrated the high-warp and low-warp workshops which were scattered in various quarters of Paris. He wanted the new factory constructed for his special purpose. With this aim in mind, he had all the buildings rebuilt so well that the work necessitated several years' time.