AN EPIDEMIC OF ADENOVIRUS TYPE-7 BRONCHOPNEUMONIA IN BANTU CHILDREN*

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Severe, often fatal, bronchopneumonia due to adenovirus types 1, 3 or 7 has been described in children in the USA, Holland, France, Japan and England.[1] Of these, some of the French[2] and Dutch[3] cases occurred in epidemics while the others were sporadic. A widespread epidemic involving 3 398 children with 528 deaths occurred in Peking[4] in 1958. Outbreaks of type-7 adenovirus infection have been described in Germany[5] and New Zealand[6] and of type 21 in New Zealand.[7]

In 1967 an epidemic of severe bronchopneumonia associated with type-7 adenovirus occurred among Bantu children who were living in subeconomic urban areas near Johannesburg. These areas have a total population of about half a million people. A prospective clinical, bacteriological and viral study was in progress when the outbreak was recognized.

During the same period type-7 adenovirus was isolated from 3 White children in the Johannesburg Children's Hospital. This, and an outbreak at the Voortrekkerhoogte Military Hospital 30 miles north of Johannesburg, indicated the widespread infection by the virus.

This paper reports the findings among the Bantu children.

MATERIALS AND METHODS

All 266 patients under 10 years of age with pneumonia admitted to 2 of the 4 paediatric wards from 26 July to 23 November 1967, were studied. It was found that 90 of these patients were suffering clinically from an adenovirus-like pneumonia. Age, weight, history and findings on physical examination were recorded. The nutritional state was assessed as 'satisfactory' or 'poor'. Those classified as 'poor' had some or all of the signs of kwashiorkor. Weights were later compared with the Boston age/weight percentile tables.[8]

The chests were X-rayed and Tine tests, haemoglobin estimations, white cell counts and differential counts were done (in 13 cases X-ray examinations of the chest and in 14 cases blood counts were not done).

Throat swabs for bacterial culture were taken on admission from 86 of the 90 patients. Forty-one patients had throat swabs and/or biopsy specimens taken for virus isolation. These specimens were carried on ice to the laboratory in a transport medium consisting of 0·5% bovine plasma albumin (Armour) in Hanks' balanced salt solution.

At the laboratory antibiotics were added and the specimens inoculated into tubes of HeLa and primary vervet kidney tissue cultures. These were maintained for 21 days, observed for cytopathic changes and haemadsorbed with guinea-pig erythrocytes. The specimens were also inoculated into the amniotic sacs of 12-day embryonated eggs and tested for haemagglutination.

Each adenovirus isolated at this period was neutralized by antiserum prepared in horses to adenovirus type-7a, strain S-1058 (supplied by the Communicable Diseases Center, Atlanta, Georgia, through the World Health Organization).

Twenty-one paired sera were obtained and examined for complement-fixing antibodies to influenza viruses A and B, para-influenza viruses 1 - 3, respiratory syncytial virus and adenovirus group antigen. Haemagglutination-inhibition tests against current influenza virus strains were done. Closed biopsy specimens of lung in 8 cases, liver in 4 cases and brain in 9 cases were taken shortly after death and inoculated into HeLa and primary vervet kidney tissue cultures for virus isolation. These specimens were also examined histologically by light microscopy and 3 of the brain biopsies by electron-microscopy.

Autopsies were done on 9 cases. Selected sections were also stained with Lendrum's stain to show inclusion bodies.

Cerebrospinal fluid was examined chemically and microscopically in 32 cases.

RESULTS

General

An adenovirus type 7 was isolated from 17 children (Table I). Ten of these patients died within 10 days of admission. Three survivors relapsed, one of whom died 4 months later of chronic pulmonary disease. Neurological symptoms were present in 9 patients, all of whom died. Nine patients had enlarged livers, of whom 2 had palpable spleens. A diagnosis of cardiac failure was made in all but one of those with hepatomegaly. Five patients were foaming at the mouth, and 7 had weights below the 3rd percentile for age.

Seventy-three children had a clinical illness very much like that of the 17 in whom adenovirus type-7 infection was proved by isolation. The findings in these 90 children are recorded in Fig. 1.

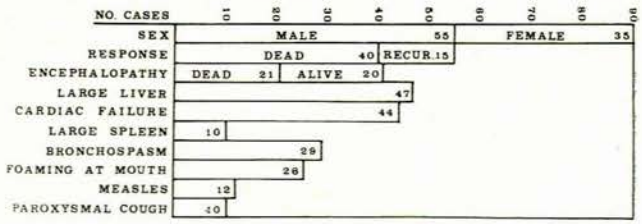

Fig. 1. Clinical features.

Clinical

Forty (44%) of these children died. Neurological symptoms were present in 41 children (45%), of whom 21 died (51%). Liver enlargement of 2 - 6 cm below the costal margin was present in 47 cases (52%), with splenomegaly in 10 (11%). A diagnosis of cardiac failure was made in all but 3 of those with hepatomegaly.

*Date received: 8 September 1970.

TABLE I. FEATURES OF 17 CASES PROVED BY VIRUS ISOLATION

Case No.	Date admitted	Age (years)	Sex	Weight (kg)	Below 3rd percentile for weight	Haemoglobin g/100 ml	White cell count thousands/mm³	Isolation: Throat swab	Isolation: Lung	Isolation: Liver	Isolation: Brain	Adenovirus reciprocal CF antibody titre: 'Acute'	Adenovirus reciprocal CF antibody titre: 'Convalescent'	CSF protein mg/100 ml	Neurological symptoms	Enlarged liver	Congestive cardiac failure	Foaming at mouth	Bronchospasm	Preceding measles	Duration of illness (days)	Response
1	23·7	7/12	M	7·8	–	8·2	5·4	Ad7				<8	<8	φ	–	–	–	–	+	–	12	Alive
2	25·7	13/12	M	8·6	–	8·7	8·5	Ad7				<8	32								20	Alive. Pneumonia again October 1967
3	22·8	1	F	7·0	+	10·5	8·0	Inf A2 Ad7							+	+	+		–	–	3	Died
4	22·8	14/12	M	7·4	++	10·1	7·3	Ad7													3	Died
5	22·8	16/12	M	8·6	++	10·0	5·9	Ad7													4	Died
6	28·8	16/12	M	10·8	–	11·2	17·7	Inf A2 Ad7	Ad7						+	+	+	+	+	–	3	Died
7	28·8	20/12	F	9·4	+	7·7	19/6	—	Ad7					76							9	Died
8	30·8	6/12	M	φ	+	7·0	52·0	Ad7						46	+	+	+	+	+	–	8	Died
9	5·9	8/12	F	5·4	+	10·2	14·1	Ad7	Ad7			<8	<8	60	+	+	+	+	+	–	6	Died. Measles antibody rise <1/20 to 1/40
10	7·9	14/12	F	10·1	+/–	11·0	28·6			Ad7				27							5	Died
11	21·9	13/12	M	10·9	–	10·1	8·0		Ad7			>128	>128	17	+	+	+	+	+	+	6	Died
12	25·9	1	M		–	8·5	13·8	Ad7														Alive. Pneumonia again November 1967
13	7·10	7/12	M	5·7	+	8·1	7·4		Ad7					89	+	–	–	–	–	–	34	Pulmonary cripple. Died February 1968
14	11·10	6/12	M	6·8	–	9·5	20·9	Ad7													4	Died
15	17·10	2	M	12·2	–	12·5	22·8			Ad7									+	–	5	Alive
16	31·10	9/12	M	5·0	–	8·8	9·6	Ad7			–	16	>128								31	Alive
17	6·11	4	F	11·6	+	9·8	25·0	HH Ad7														Alive

* Clinically assessed as well nourished.
/ Clinically assessed as poorly nourished.
φ Not done or unavailable.
Ad7 = adenovirus type 7; HH = herpesvirus hominis; Inf. A2 = influenza A2 virus.

Bronchospasm was severe in 29 (32%) cases. Twenty-six patients had white foam at the mouth, of whom 10 (11%) had a pertussis-like cough. In 12 (13%) children a history of a preceding measles-like rash was obtained. The Tine test was negative in all the children.

Nutrition was assessed as 'poor' in 26 cases (29%). On comparing weight for age on the Boston percentile tables for privileged children, 45 (50%) were below the 3rd percentile (Fig. 2).

The peak age incidence lay between 6 and 15 months (Fig. 3), the youngest being 2 months and the oldest 9 years of age. The fever lasted from 2 to 22 days, the average duration being 6 days. Thirty-four children remained severely ill for more than 7 days. The longest episode of severe illness lasted 35 days. Recurrences of bronchopneumonia occurred in 15 of the 50 (30%) survivors.

Radiology

The chest radiographs showed a pattern varying from interstitial nodulation or hyperinflation alone to extensive bilateral consolidation with hilar adenopathy. Bilateral patchy opacities were most commonly seen.

Bacteriology

Throat swabs were taken from 86 children. *Escherichia coli* was isolated from the swabs of 33 (38%) children, and *Staphylococcus aureus* and klebsiellae (9 *K. aerogenes,* 1 *K. edwardii*) from 10 (12%) children each. Throat swabs of 62 children taken during a non-epidemic period yielded isolates of *E. coli* from 17 (27%), *S. aureus* from 5 (8%), klebsiellae from 26 (22 *K. aerogenes,* 4 *K. edwardii*) and *Streptococcus pneumoniae* from 9 (15%). No antibody rise to *Haemophilus pertussis* was demonstrated by agglutination test in paired sera from 13 children. High-titre antibodies were found in case 9 who had not been immunized to *H. pertussis.*

Haematology

Seventy-six patients had blood taken for haematological examination. A hypochromic anaemia was present in 32 cases. The mean haemoglobin was 9·2 g/100 ml with a range from 4·7 to 13·3 g/100 ml (age-corrected percentage of normal values: mean 76%, range 39 - 104%). Fifty pneumonia cases of the previous year showed a mean of 10·6 g/100 ml (79% of normal) with a range from 6·2 to 14·4 g/100 ml (53 - 116% of normal).

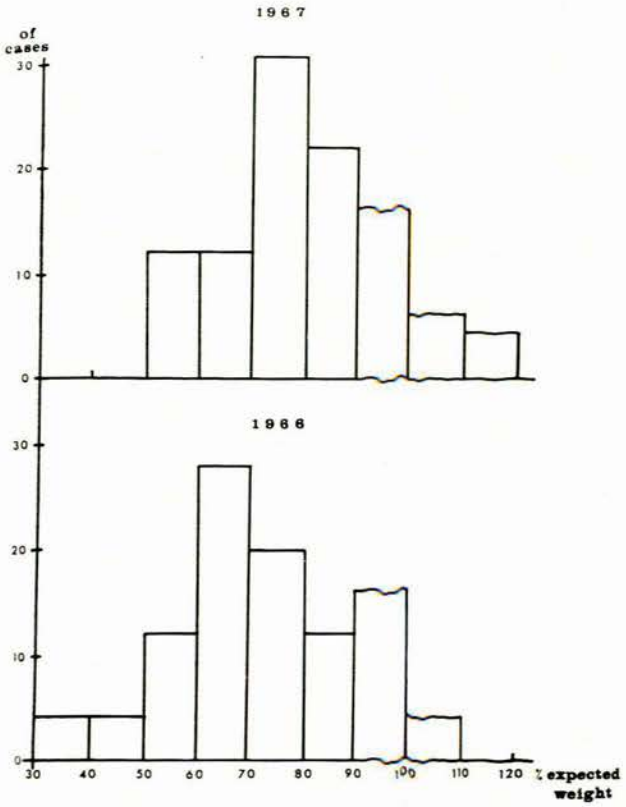

Fig. 2. Nutrition in pneumonia (July - November).

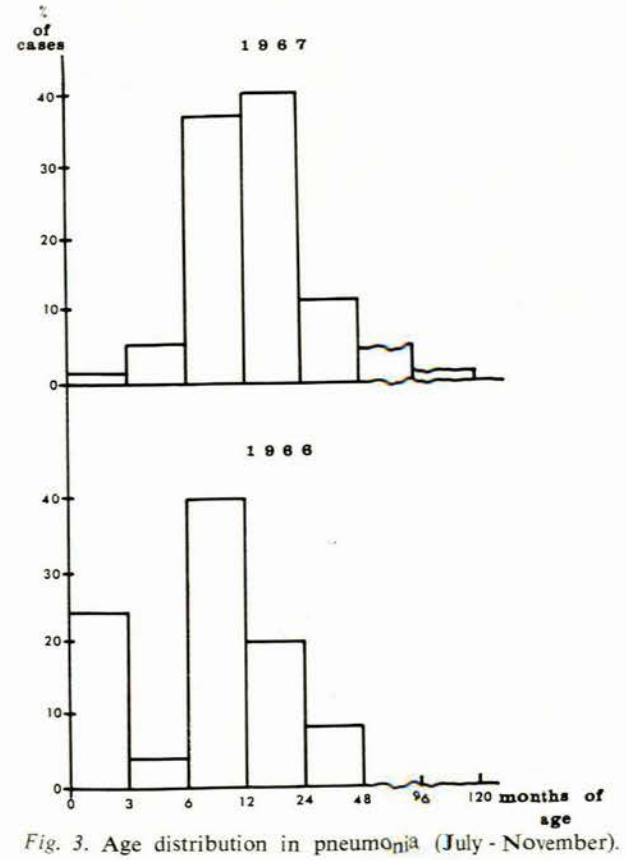

Fig. 3. Age distribution in pneumonia (July - November).

The white cell counts varied between 1 400 and 71 000 cells/mm³ while for pneumonia cases of the year before the values ranged between 3 000 and 38 000 cells/mm³. The two groups showed a very similar distribution with most of the counts lying between 50 and 150% of average normal for age. In 6 cases of 60 in whom a differential count was done there was an absolute lymphocytosis. An associated neutrophilia was seen in 5 of these cases and an isolated neutrophilia was seen in 13 cases.

Cerebrospinal Fluids

In 32 patients the cerebrospinal fluid was examined microscopically and chemically. Sixteen fluids had a protein content of over 45 mg/100 ml, the range being from 13 to 204 mg/100 ml. The cell count was always less than 5 cells/mm³. In one case the sugar content was 22 mg/100 ml, while the remainder were higher than 40 mg/100 ml.

Virology

During the months of the epidemic, virus isolation was attempted from throat swabs or biopsy specimens or both, from 41 cases. From 17 children adenovirus type 7 was isolated (11 isolations from 32 throat swabs, 6 from 8 lung aspirates and 2 from 4 liver aspirates) (Table I). Two strains of influenza viruses A2/Jhb/67 and one of herpes simplex virus were isolated from children in whom adenovirus type 7 was also isolated. A para-influenza virus type 2 only was isolated from one patient. A four-fold or greater antibody titre increase to adenovirus was shown in 2 of the 5 paired sera of the cases from whom an adenovirus was isolated. In one a measles antibody rise was noted and high antibody titres to adenoviruses in a further case. Five patients from whom no virus was isolated showed adenovirus antibody titre rises. Brain aspirates from 9 patients were studied, 5 of whom had yielded an adenovirus type 7 from other specimens. No virus was isolated from the brain aspirates. Electron-microscopy of 3 brain aspirates did not show any virus particles.

Postmortem Findings

Nine cases underwent postmortem examination. Seven cases showed a congested upper respiratory tract. The lungs were oedematous and haemorrhagic with hilar gland enlargement in all cases. Histologically, an extensive necrotizing bronchopneumonia with intra-alveolar haemorrhage, macrophages in the alveoli, destruction of the bronchiolar epithelium and widespread small-vessel congestion were seen (Fig. 4). Proliferative changes were also seen, though they were not prominent. Typical intranuclear inclusions were seen in the alveolar and bronchial epithelial cells. These changes agree with those found by Wright *et al.*,[1] Chany *et al.*,[2] Hsuing[4] and Becroft.[6] The heart was dilated and enlarged in 3 cases.

The brain was markedly congested with microscopic haemorrhages in 5 cases (Fig. 5).

A REPRESENTATIVE CASE DESCRIPTION

A female infant of 8 months was admitted on 5 September 1967, with a 3-day history of cough, vomiting and foaming at the mouth. A twin sister had died of a similar illness a week before. The infant was poorly nourished and weighed 5·4 kg (12 lb). She was cyanosed and dyspnoeic with grunting respiration and the temperature was 104°F with pulse and respiratory rates of 180/min and 80/min respectively. The conjunctivae

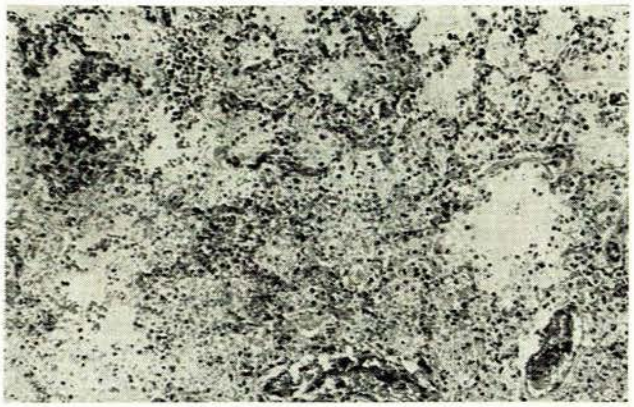

Fig. 4. The changes in the lungs at postmortem examination of one of the cases, J.M. (H. & E. × 95).

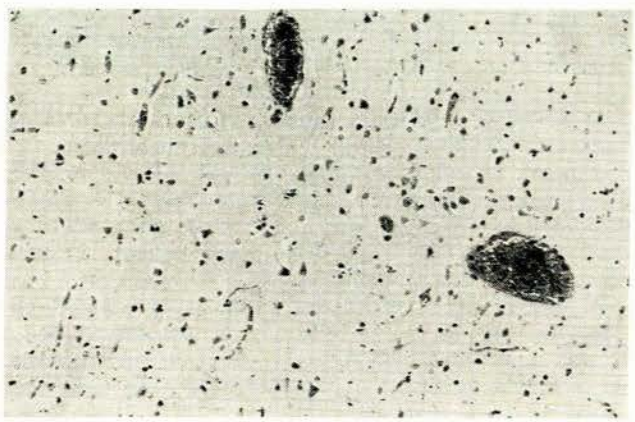

Fig. 5. The congested brain seen in case S.R. at postmortem examination (H. & E. × 95).

were suffused. Bilateral crepitations and bronchospasm were present and the liver was enlarged to 5 cm below the costal margin. Generalized spasticity together with opisthotonus and deviation of the eyes to the right were noted. The haemoglobin level was 10·2 g/100 ml and the white cell count 14 000/mm³ with 70% neutrophils and 30% lymphocytes. The cerebrospinal fluid contained 2 lymphocytes/mm³ and the protein and sugar contents were 60 mg/100 ml and 87 mg/100 ml respectively. Plasma electrolyte levels were within normal limits. *Klebsiella aerogenes* was cultured from a throat swab but a simultaneous blood culture was negative. The infant remained pyrexial and tachypnoeic with increasing bronchospasm. Digoxin, ampicillin and cloxacillin were ineffective and the child died on the 6th day in hospital. Adenovirus 7 was cultured from a throat swab and also from a lung biopsy specimen taken shortly after death. No virus was grown from the brain aspirate. Permission for autopsy was not obtained.

DISCUSSION

A greater than 3-fold increase in the number of cases of pneumonia admitted to hospital in late winter and spring of 1967, relative to the previous year gives an indication of the size of the epidemic.

The clinical presentation was so striking that a peculiar disease was suspected within 2 weeks of the outbreak. A fulminating pneumonia associated with an encephalopathy in almost half the cases and a distressing lack of response to treatment were seen. The cerebral signs were mainly convulsions, neck retraction and coma.

This encephalopathy coupled with a raised cerebrospinal fluid protein level was the striking complication in this epidemic. It has been noted previously by Hsuing,[4] Chany *et al.*[2] and Lang *et al.*,[7] but never had the incidence been so high. This may be partly due to the fact that only hospitalized cases were considered. The cause of the encephalopathy remains uncertain. Virus was not isolated from the brain in this epidemic although Chany *et al.*[2] were successful in doing so. The only consistent reaction in the brains was congestion with microscopic haemorrhages.

Hypoglycaemia did not account for the neurological signs. It is difficult to assess what effect anoxia and respiratory acidosis may have had on the brain function. It must be noted, however, that increased ventilation and the administration of oxygen and sodium bicarbonate had no effect on these children. The small-vessel haemorrhages which were distributed throughout the body, including the cerebral vessels, may be relevant. Hepatomegaly associated with cardiac failure was common.

Intravenous therapy was often needed as a result of diarrhoea and vomiting. Severe bronchospasm and foaming at the mouth was seen in just under one-third of the cases. We have since noticed foaming with bronchospasm in other respiratory viral infections. This could be expected in view of the widespread lung damage and exudation found at postmortem examination. In no case was a distinct whoop heard, although 11% had paroxysms of coughing ending in vomiting, and some of the white cell counts were very high. Temperatures were high, often for a week and more. The acute illness was long and many of the survivors came back with recurrences of pneumonia. This finding, together with subsequent bronchiectasis, has also been noted by Lang *et al.*[7]

Digitalization, steroids and humidification of the atmosphere were often used but appeared to bring little or no relief. There was no response noted from assisted respiration and intravenous sodium bicarbonate. As indicated previously, antibiotics had no apparent effect on the course of the illness. This is emphasized by the bacteriological results where the occurrence of presumed pathogens in the throat was clearly less frequent than at other times. The fewer bacteria found in the throats of these cases indicate the lesser importance of bacterial infection in these cases and suggest, together with the lack of response to antibiotics, that the pulmonary damage was induced by the virus.

Malnutrition has been suspected as being a contributory cause in adenovirus infection by Chany *et al.*,[2] Hsuing,[4] and Lang *et al.*[7] In the population studied this is a constant problem but it is the first time that such an epidemic appears to have occurred. In addition, by comparison with the previous year's pneumonia cases, those suffering from adenoviral infection were significantly better nourished (Fig. 2).

The peak age incidence of pneumonia occurred soon after maternal adenovirus antibody has normally disappeared.[9]

The high incidence of preceding clinical measles and influenza virus A2 infection suggests, as noted in the Chinese outbreak, that the pathogenicity of the adenovirus is increased when infection occurs in an already damaged respiratory tract.

SUMMARY

An adenovirus type-7 epidemic occurred in a South African Bantu child population. The major clinical findings of a fulminating pneumonia with a high death rate and with slow resolution in the survivors are similar to previously reported series. A feature in this group was the high incidence of encephalitis. No correlation with the nutritional state of the children could be found.

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