A SURVEY OF PRIMARY INFANTILE AND JUVENILE PNEUMONIA *

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Statistical review

The material for review was collected from the records of three Dublin Hospitals for the years 1937 to 1939. All patients dying within twenty-four hours of admission, or in whom signs of improvement had set in before starting treatment, were excluded. The cases were clinically divided into the two groups of lobar and atypical pneumonia. The former showed clinical evidence of lobar consolidation, the latter consolidation of an irregular patchy nature. Eight hundred and ninety-five cases were studied. Table 1 shows the age group distribution, and table 2 the combined fatality rates for the three years studied.

TABLE 1

	AGE (YEARS)	CASES
ATYPICAL PNEUMONIA	0-1	336
	1-2	160
	2-12	123
		619
LOBAR PNEUMONIA	0-1	59
	1-2	72
	2-12	145
		276

TABLE 2

CLINICAL TYPE	CASES	DIED	CASE-MORTALITY PER CENT.
All types	895	177	19.8
Atypical	619	150	24.2
Lobar	276	27	9.8

The great importance of age in relation to death rate is well shown in table 3.

* Based on a Thesis for the degree of M.D., University of Dublin.

TABLE 3
AGE GROUP CASE-MORTALITY 1937 TO 1939

AGE	MONTH GROUPS					YEAR GROUPS		
	0-1	1-3	3-6	6-9	9-12	1-2	2-6	6-12
No. treated	19	61	88	97	130	232	182	86
Died	13	24	27	16	28	47	19	3
Mortality per cent. ..	68.4	39.3	30.6	16.5	21.5	20.2	10.4	3.5

The relationship of the clinical type of the disease to the death rate in Dublin is shown in table 4.

TABLE 4
AGE GROUP CASE-MORTALITY RATES FOR LOBAR AND ATYPICAL PNEUMONIA 1937-1939

LOBAR AGE GROUP	MONTH GROUPS					YEAR GROUPS			TOTAL
	0-1	1-3	3-6	6-9	9-12	1-2	2-6	6-12	
No. of cases	2	6	9	13	29	72	83	62	276
Deaths	2	2	4	2	2	8	6	1	27
Mortality per cent. ..	100	33.3	44.4	15.4	6.9	11.1	7.2	1.6	—
ATYPICAL AGE GROUP	MONTH GROUPS					YEAR GROUPS			TOTAL
	0-1	1-3	3-6	6-9	9-12	1-2	2-6	6-12	
No. of cases	17	55	79	84	101	160	99	24	619
Deaths	11	23	22	26	22	33	13	0	150
Mortality per cent. ..	64.7	41.8	27.8	30.9	21.8	20.9	13.1	0	—

It will be noticed that clinical lobar pneumonia in infants of the 0-6 months age group is comparatively rare, but that when it does occur it tends to carry with it a death rate as high as that of atypical pneumonia; thereafter atypical pneumonia is about twice as fatal as lobar.

The importance of pneumonia as a social danger to the children of the Irish Free State is shown by reference to the official statistics published by the Eire Government. These show that in 1936 and 1937 of every 1,000 children born at full term in Eire, 8.96 and 8.34 respectively died of certified pneumonia under one year of age. The disease ranks third as the greatest slayer of full-time infants in Dublin in the first year of life.

Clinical evidence has now firmly established the value of chemotherapeutic treatment in the adult pneumonias, but little evidence has yet been collected of the value or otherwise of chemotherapy in treating the pneumonias of infants and young children.

Tables 5 and 6 were drawn up after careful study of the records of three Dublin hospitals.

TABLE 5
ANNUAL CASE-MORTALITY RATES FROM LOBAR AND ATYPICAL
PNEUMONIA IN CHILDREN AGED 0-1 YEAR

LOBAR PNEUMONIA			
	1937	1938	1939
Cases	8	32	19
Died	0	11	7
Mortality per cent. .. .	0	34.4	36.8

ATYPICAL PNEUMONIA			
	1937	1938	1939
Cases	74	134	118
Died	31	49	29
Mortality per cent. .. .	41.9	36.6	24.6

TABLE 6
ANNUAL CASE-MORTALITY RATES FROM LOBAR AND ATYPICAL
PNEUMONIA IN CHILDREN AGED 1-2 YEARS

LOBAR PNEUMONIA			
	1937	1938	1939
Cases	16	37	19
Died	3	8	4
Mortality per cent. .. .	18.47	21.6	21

ATYPICAL PNEUMONIA			
	1937	1938	1939
Cases	24	80	56
Died	5	17	11
Mortality per cent. .. .	20.8	21.3	19.6

The number of cases makes statistical deductions inconclusive, but there would appear to have been a tendency for the death rate from atypical pneumonia in the first year of life to be lowered, whilst the rates in lobar pneumonia for the first two years of life appear to have been unaffected. As these figures appeared unsatisfactory compared with the reported results from the newer methods of therapy in the adult pneumonias, an investigation of the results of individual methods of treatment in these three hospitals was undertaken (table 7).

TABLE 7
PERCENTAGE CASE-MORTALITY FOR VARIOUS METHODS OF
TREATMENT, IN CHILDREN AGED 0-12 YEARS

TREATMENT	CASES	DIED	PERCENTAGE MORTALITY
Symptomatic.. ..	460	101	21.9
M and B 693	158	33	20.9
M and B 693+Serum	163	16	9.8
Serum	54	18	33.3
Sulphanilamide	12	5	41.7
Vaccine	48	12	25

Serum=Felton's anti-pneumococcal horse serum Types 1 and 2.

Vaccine=Compound pneumococcal, streptococcal and H. influenzae vaccine, prepared by Evan's Biological Institute.

From this table, it will be seen that the best results may be expected from the combined use of sulphapyridine with anti-pneumococcal serum, and that in the very young, chemotherapeutic measures alone may not offer the best chances of recovery. This point depends largely on two factors, viz. differences in immunity factors in children, and differences in the anatomico-pathological type of disease in young children.

Immunity factors in children

The principal antibody mechanisms involved in pneumococcal infections are agglutination and precipitation. Complete dissolution of the organisms is impossible without additional phagocytic activity, but there is no evidence to show that such activity is lacking in infants.

Fleming (Fleming, 1938; Maclean, Rogers and Fleming, 1939) has shown that the addition of a specific antibacterial serum to a mixture of blood and M and B 693 increases its antibacterial action to pneumococci, and has further substantiated these findings by experiments in mice and rabbits (1939). The function of the specific antiserum is the neutralization of the specific soluble substance, which is the toxic substance proper of the pneumococcal capsule. This neutralization occurs in the circulation and peripheral organs (Kempf and Nungester, 1939), and apparently follows a mathematical ratio. The following experiment was carried out in order to determine whether the very young produce such antibacterial substances or not.

Technique. A slide agglutination technique, described by Bullowa (1937), was used. A drop of the patient's serum was mixed with a drop of the specific antigen consisting of killed suspensions of pneumococci, two billions per c.c. on glass slides. Antigens of types 1, 2, 3, 4, 5, 6, 7, 8 and 14 pneumococci were used. Slides were air cooled and fixed in a solution of 94 c.c. water, 1 c.c. glacial acetic acid, 5 c.c. formalin (40 per cent. formaldehyde). When dried they were stained for a few seconds with Löffler's alkaline methylene blue stain, dried and examined by 1/12 oil immersion lens. Control slides were also put up consisting of (i) saline or normal blood with antigen; (ii) antigen with type specific serum of known agglutination titre. The agglutination is symbolically expressed as one of four degrees : —, =, =, —.

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A special polyvalent pneumococcal vaccine containing all the thirty-two types of pneumococci with several strains of certain types, was given by subcutaneous injection to healthy subjects of various ages, and their sera were examined by the above technique on the third and seventh days following inoculation. Injections were given on three successive days as follows: 0.1 c.c. 0.2 c.c. and 0.4 c.c. The vaccine contained 100 million organisms per 0.1 c.c., and was prepared by Professor Alexander Fleming in the Inoculation Department of St. Mary's Hospital, London.

Results. Table 8 shows the results in six subjects aged eight weeks to fourteen years.

TABLE 8
THIRD DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTI- NATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	—	—	—	—	—	—	+	—
2	—	—	—	—	—	—	+	—
3	—	—	—	—	—	—	+	—
4	—	—	—	—	—	—	+	—
5	—	—	—	—	—	—	+	—
6	—	—	—	—	—	—	+	—
7	—	—	—	—	—	—	+	—
8	—	—	—	—	—	—	+	—
14	—	—	—	—	—	—	+	—

SEVENTH DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTI- NATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	—	—	—	—	—	—	+	—
2	—	—	—	—	—	—	+	—
3	—	—	—	—	—	—	+	—
4	—	—	—	—	—	—	+	—
5	—	—	—	—	—	—	+	—
6	—	—	—	—	—	—	+	—
7	—	—	—	—	—	—	+	—
8	—	—	—	—	—	—	+	—
14	—	—	—	—	—	—	+	—

Patient 1 Age 5 years.
 „ 2 „ 8 „
 „ 3 „ 14 „
 „ 4 „ 3 „
 „ 5 „ 8 weeks.
 „ 6 „ 2 years.

Table 9 shows the results of six subjects aged six years to sixty-eight years using doses of 0.2, 0.5 and 1.0 c.c. respectively at the same time intervals.

TABLE 9
THIRD DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTI- NATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	—	—	—	—	—	—	+	—
2	—	—	—	—	—	—	+	—
3	—	—	—	—	—	—	+	—
4	—	—	—	—	—	—	+	—
5	—	—	—	—	—	—	+	—
6	—	—	—	—	—	—	+	—
7	—	—	—	—	—	—	+	—
8	—	—	—	—	—	—	+	—
14	—	—	—	—	—	—	+	—

No. 2 was a patient suffering from a Lederer's anaemia.

SEVENTH DAY TITRATION

ANTIGEN TYPE	SUBJECTS						ANTIGEN SPECIFIC AGGLUTI- NATING SERA	ANTIGEN SALINE
	1	2	3	4	5	6		
1	—	—	—	—	—	—	+	—
2	—	—	—	—	—	—	+	—
3	—	—	—	—	—	—	+	—
4	—	—	—	—	—	—	+	—
5	—	—	—	—	—	—	+	—
6	—	—	—	—	—	—	+	—
7	—	—	—	—	—	—	+	—
8	—	—	—	—	—	—	+	—
14	—	—	—	—	—	—	+	—

+ titres ranged according to type from 1/5 to 1/60.

Patient 1	..	..	..	Age 56 years.
.. 2	..	..	..	.. 39 ..
.. 3	..	..	..	.. 4 ..
.. 4	..	..	..	.. 68 ..
.. 5	..	..	..	.. 12 ..
.. 6	..	..	..	.. 6 ..

These experiments tend to show that the anti-pneumococcal antibody-producing mechanism of very young children is incapable of producing the necessary immunological substances necessary to complete the destructive powers offered by chemotherapy alone. In adults, sensitizing doses of pneumococci inhaled from time to time have given to the antibody mechanism the potential energy necessary to bring it rapidly into action when pathogen-producing organisms gain entry into the tissues. Sulphapyridine in adults often kills the pneumococci so rapidly and effectively that the stimulus to antibody production is eliminated. This may explain the delayed resolution so often seen in such cases. It is important to maintain therapeutic levels of the

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drug in the blood stream for seven to ten days. There is evidence to show that in adults sulphathiazole (Kneeland and Mulliken, 1940) may prove a better drug because, being less rapidly bactericidal, there is more opportunity for the immunity mechanism to come into action. This should tend to prevent acute relapse and perhaps delayed resolution. This brings out the important point that the assessment of treatment in the pneumonias of children should be considered strictly from the age group point of view. Once a child passes the age of two years it enters, immunologically speaking, the realm of the adult pneumonias. The reason for this is not only a change in the mode of the immunity response, but also a change in the anatomic-pathological type of the disease. Table 10 taken from Reimann's book on the pneumonias (1938) shows this clearly.

TABLE 10
RELATIVE INCIDENCE OF LOBAR AND ATYPICAL PNEUMONIA IN CHILDREN
(From various authors)

			IN ALL CHILDREN		CHILDREN UNDER TWO		CHILDREN OVER TWO	
			NUMBER OF CASES	PER-CENTAGE	NUMBER OF CASES	PER-CENTAGE	NUMBER OF CASES	PER-CENTAGE
Lobar	..	..	1,144	76	437	60	707	92
Atypical	..	..	362	24	300	40	62	8

The same author points out that lobar pneumonia has a surprisingly low death rate in later childhood but is considerably more dangerous in infants. Pneumococcal pneumonia in general is about three times as fatal in children less than two years of age as in older ones.

In view of these findings the present position of pneumonia occurring in this all-important age group of 0-2 years of age may be considered. Eighty-two per cent. of the 106 cases dying from pneumonia in these three hospitals in 1937 and 1938, and sixty per cent. of the forty cases dying in 1939, were in children under one year of age. Has there been a bettering of the lot of these very young patients in recent years? A glance at table 11, prepared from the records of the three hospitals, shows that the answer is both yes and no. There has been an actual increase in the fatality rates from lobar pneumonia whilst there has been a steady fall in the death rates from the atypical forms.

Methods of therapy in infantile pneumonia

The chief reasons for the apparent failure of the newer therapy in infantile pneumonia is that too much reliance is placed on chemotherapy alone, and that no effort is made to better the developing immunity mechanisms by the giving of serum. To establish this point the results of various treatments in a

TABLE 11
ANNUAL MORTALITY RATES FROM PNEUMONIA IN CHILDREN AGED
0-2 YEARS

	1937			1938			1939		
	CASES	DIED	MORTALITY PER CENT.	CASES	DIED	MORTALITY PER CENT.	CASES	DIED	MORTALITY PER CENT.
Lobar ..	24	3	12.5	69	19	27.2	38	11	28.9
Atypical	98	36	36.7	214	66	30.8	174	40	22.9

series of very young children must be carefully studied. Serum is indeed expensive (approximately £10 to £20 worth are necessary for treating a severe case of pneumonia in an adult) but as Reimann economically puts it, 'When one compares its cost with the cost of an operation for appendicitis, the mortality of which is far less than that from pneumonia, the price is indeed not excessive. Furthermore, the shortening of the duration of the pneumonia and reduction in the number of days spent in hospital and in expense of nursing, result in savings which often overbalance the cost of serum.' All children with pneumonia who are under two years of age should be admitted to a properly equipped hospital as soon as the diagnosis is made. There are three reasons for this: Firstly, the giving of serum intravenously to infants requires considerable skill. Secondly, there is now substantial evidence that small blood transfusions help these patients over a severe infection; and thirdly, the danger of sudden dehydration with its devastating after effects requires careful watching and immediate counteraction by the administration of parenteral fluids. Cyanosis may necessitate the use of an oxygen tent. In a large city, a special team could be got together as an independent unit of a hospital for dealing with all cases of infantile pneumonia.

Dr. F. C. McDonald of the Boston Floating Hospital has shown (1939) what excellent results may be obtained by good symptomatic treatment and skilled nursing. His method is to give oxygen and sedatives liberally and to ensure an adequate intake of food, fluids, glucose and vitamin concentrates (A, B, C and D). Except when breathing is made difficult by tenacious sputum, a pleural effusion or pharyngeal complications, he gives morphine freely, his dosage being 1/24 grain at 15 lb., 1/12 grain at 30 lb. and 1/6 grain at 75 lb. The use of morphine in this way requires great judgment.

Special considerations. Since sulphapyridine is insoluble in relatively neutral solutions, its absorption from the gut is likely to be influenced by the changes in pH which fluids may undergo in the small intestine, and by the varying rapidity with which fluids may pass along the gut in health and disease. If diarrhoea or vomiting is present there will not only be a loss of sulphapyridine from the bowel or stomach but the actual amount of fluid in the bowel may be so reduced as to render the solution of an adequate therapeutic amount of the drug impossible. Again, if the bacterial flora of the bowel is such as to reduce

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the pH of its contents, solubility of sulphapyridine may also be reduced. Thus, apart from combating dehydration and acidosis, the parenteral administration of glucose-saline with sodium sulphapyridine has an important rôle in therapy. In such an acute disease as pneumonia it may be advisable in severe cases to control the level of blood sulphapyridine by chemical estimation. The method described by Werner (1939) is an admirable one for clinical purposes. Using this method, I found that adequate blood levels of the drug could be maintained in the average case by giving the following dosage:

AGE					DOSAGE OF M AND B 693
0-3 months	..	..	..	..	$\frac{1}{4}$ tablet every 4 hours.
3-6 months	..	..	..	..	$\frac{1}{2}$ tablet every 6 hours.
6 months-1 year	..	..	..	..	$\frac{1}{2}$ tablet every 4 hours.
1-2 years	..	..	..	..	1 tablet three times a day.

These findings closely agree with the dosage worked out by Hynes (1940) at the Hospital for Sick Children, Great Ormond Street.

In poorly nourished and maldeveloped children, a severe acute secondary anaemia is liable to occur, especially in the presence of septicaemia or when chemotherapy is given over a prolonged period. Such anaemia reduces considerably the immunity response. Early blood transfusion is often a life-saving procedure in such cases. The general response of the child to treatment should be the main guiding factor for its use, since haemoglobin estimations are often misleading owing to the variation of blood-concentration which occurs in severely sick children.

The use of type specific serum is important. Curnen (1939), at a meeting of the Massachusetts Medical Society, gave a report on thirty-four cases of type XIV pneumonia in children of whom twenty-two were under two years of age, treated with type specific serum alone. All survived, and all but three with complications or a mixed infection responded promptly to adequate doses of the serum. Bullowa had an 8.5 per cent. mortality in 330 cases between 1934 and 1937.

Don et al., 1940 have shown that the best results in adults with pneumococcal septicaemia are obtained by the use of specific serum combined with chemotherapy. There is a 100 per cent. mortality amongst untreated cases of pneumococcal septicaemia in children under two years of age. The necessity of combined therapy is therefore most urgent in young children with pneumococcal septicaemia.

Special mention should be made of pneumonia occurring in malnourished, underdeveloped or premature infants. Modern methods of treatment have given these a better chance of recovery, but the necessity of maintaining nutrition whilst the struggle is in progress is still of vital importance. Breast feeding should be continued if practicable, but if this is impossible, fresh or stored breast-milk from a healthy donor, preferably the mother, should be obtained.

Non-pneumococcal pneumonias

Poor laboratory technique may fail to show the presence of other primary or secondary pathogenic organisms. In children under twelve years of age

60 to 70 per cent. of non-pneumococcal pneumonias are due to streptococci and about 6 per cent. to staphylococci. B. Friedlander pneumonia in young children is practically unknown. If after forty-eight hours of combined sero-chemotherapy, there has been no clinical amelioration of the symptoms, further bacteriological evidence must be sought to confirm the nature of the pathogen responsible. It is in such cases that lung suction is of great value. Bullowa in four years did 405 lung suction in children, and 122 cases gave a growth. Pneumothorax was the only complication. If streptococci appear responsible, the use of sulphanilamide should be considered. No mention will be made of the acute tuberculous pneumonias or any of the rarer acute primary pneumonias of children.

Prognosis

The four most important factors in determining prognosis are: (i) the age of the child, (ii) the time of starting treatment, (iii) the general condition of the child at the onset of the pneumonia, and (iv) the treatment given.

The chances of recovery in children over the age of two years, are as good as those of a young adult. If the child is under two years of age difficulties and failures are likely to be encountered. If specific treatment is delayed, the prognosis will follow the lines of a case of perforated peptic ulcer, in which the passing of every hour without treatment brings the patient nearer to death. Poorly developed, undernourished and premature children have the worst prognosis.

Summary

A review of 895 cases of juvenile pneumonia in Dublin for the years 1937 to 1939 is given. The age of the patient and the pathological type of causative organism are still of great importance in determining prognosis. There appears to have been a lowering of the death rate from atypical pneumonia in the first year of life since the introduction of chemotherapy, but the results in treating lobar pneumonia by chemotherapy alone in infants are disappointing. Statistical and experimental studies suggest that the administration of serum with chemotherapy in the infantile pneumonias gives the best results. Experiments indicate that the anti-pneumococcal immunity mechanism is relatively weak in infants. Children over two years of age with pneumonia can be treated in a similar manner to adults. All infants under two years of age with pneumonia should be treated in a properly equipped hospital. Blood transfusion, parenteral fluids, oxygen, sedatives and skilled nursing are almost as valuable as chemotherapy in severe cases of pneumonia in infants. They are particularly important in premature and poorly nourished children. The importance of maintaining weight during treatment is emphasized; efforts to continue breast feeding should be made. Prognostic factors are discussed.

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