*J. Hyg., Camb.* (1975), **75**, 315
*Printed in Great Britain*



# An investigation of the family background of acute haemophilus infections of children

By D. C. TURK

*Bacteriology Department and Regional Public Health Laboratory, Radcliffe Infirmary, Oxford OX2 6HE*

(*Received* 7 *April* 1975)

## SUMMARY

Nose and throat swabs, for culture of *Haemophilus influenzae* type b, and blood samples, for measurement of antibodies specific for that serotype, were collected from members of 28 families from which children had been admitted to hospital with acute *H. influenzae* type b infections (mainly meningitis or epiglottitis). The patients with meningitis were younger than those with epiglottitis and had more siblings, with a marked predominance of sisters. Investigations within a few days of admission of the affected children to hospital detected carriers of *H. influenzae* type b (19 altogether) in 13 of the 28 families, including 9 of the 13 families with 3 or more children. Members with raised antibody titres for *H. influenzae* type b (suggesting the presence of the organism for at least a few weeks) were found in 17 of the 25 families from which blood samples were obtained, including all 11 families with 3 or more children. Most of the patients probably acquired their infections from within their own families, and siblings under 11 years old were of predominant importance both as carriers and as potential sources of the patients' infections. Persistence of the organism within families for up to 6 months was demonstrated. Possible reasons for the difference in age-incidence between haemophilus meningitis and epiglottitis and for the occurrence of the former in babies with older sisters are suggested, and also a possible connexion between the results of this survey and the likely value of immunization against *H. influenzae* type b.

## INTRODUCTION

A minority of strains of *Haemophilus influenzae* are capsulated (Pittman, 1931). These capsulated strains can be divided into six serotypes, of which type b is both the commonest and also the most important; strains of this type (but only rarely those of any of the other types) can cause various acute and often serious illnesses, usually in young children (Alexander, Ellis & Leidy, 1942; Turk & May, 1967; Sell, 1970). *H. influenzae* type b meningitis is well known in most parts of the world; in the U.S.A., where in recent years it has been the commonest form of bacterial meningitis, there are probably about 8000 cases a year (Bennett, McCormick & Feldman, 1974). Other less common diseases due to *H. influenzae* type b include epiglottitis, pneumonia, suppurative arthritis and cellulitis.

Surveys of nasopharyngeal carriage of *H. influenzae* type b in healthy people have usually indicated carriage rates around 3% for children under 5 years old and around 1% for older children and adults, though much higher rates have been found in closed communities of young children (Johnson & Fousek, 1943; Dawson & Zinnemann, 1952; Masters, Brumfitt, Mendez & Likar, 1958; Turk, 1962, 1963; Mpairwe, 1970). It is probable that carriage of a capsulated *H. influenzae* strain by individuals seldom lasts for more than a few months (Turk, 1962); maintenance of a 3% carriage rate for type b among young children seems therefore to require that a much higher proportion of them carry it at some time. The prevalence of antibodies for *H. influenzae* type b in sera of adolescents is in keeping with this idea (Fothergill & Wright, 1933; Smith, Ingram, Smith, Gilles & Bresnan, 1973). Sell, Turner & Felderspiel (1973), who collected frequent nasopharyngeal swabs from 104 normal children during their early years of life, isolated *H. influenzae* type b at some time from 38·5% of them before they were 5 years old, and presumably there were others who carried it but escaped detection. So it is clear that an encounter with this organism is to be regarded as a normal part of the process of growing up in a human community. Why then is it only an occasional child who develops a significant illness as a result of this encounter? And what factors determine the nature of the disease that a particular child develops?

Partial answers to these questions may lie in bacteriological features of the patient's home environment. Ounsted (1950) found that children with haemophilus meningitis more often had two or more older siblings under the age of 12 years than did children of similar age admitted to hospital for other reasons, including meningococcal meningitis. He postulated that the haemophilus needed passage through one or two partially immune contacts before 'a strain is evolved that can pass the meningeal barrier'. Good, Fousek, Grossman & Boisvert (1943) investigated the home contacts of children from whom *H. influenzae* type b had been isolated at the time of their admission to hospital; they isolated strains of this type from 6 out of 7 siblings under 8 years old in the homes of 5 children whose illnesses were attributable to these organisms, whereas they found no carriers of this serotype in the homes of 3 children whose type b strains did not appear to be doing them any harm, or in the homes of 6 other 'control' children whose admission swabs had not grown *H. influenzae* type b. Commenting on these findings and on my own isolation of *H. influenzae* type b from 2 of the 8 available parents and from 7 of the 14 siblings of 6 Jamaican children admitted to hospital with haemophilus meningitis, I wrote that they did not permit 'the deduction that an abnormally high carriage-rate for *H. influenzae* type b precedes and gives rise to a case of meningitis. It could be that the affected child in the early stages of the disease is a potent source of infection for others in the household... It may be possible to obtain retrospective information about the sequence of events by repeated measurements of type-specific antibodies in the blood of members of the family after the case has occurred' (Turk, 1963). Since then I have investigated other families from which children had been admitted to hospital with *H. influenzae* type b infections, and I here report the results from 28 such families. Investigations of 25 of these included examination of blood samples from at least some of their members for

antibodies to *H. influenzae* type b. In the light of current thought about the propriety of collecting blood samples for research purposes from healthy children, this series of investigations is now at an end.

## THE FAMILIES STUDIED

Twelve of the 28 families were those of children admitted to the Royal Victoria Infirmary, Newcastle-upon-Tyne, in the years 1962–9; of these 12 children, 7 had meningitis, 2 had epiglottitis and 3 had suppurative arthritis (a girl with interphalangeal joint infection, previously reported by Miller & Turk (1965), a boy with arthritis of the ankle and another boy with arthritis of the knee). The other 16 families were those of children admitted to the Radcliffe Infirmary, Oxford, in the years 1970–4; in all, 19 children from these families were admitted with *H. influenzae* type b infections – the 16 index cases (7 of meningitis, 8 of epiglottitis and one of severe conjunctivitis and probable orbital cellulitis which was previously reported by Cartwright & Turk, 1974) and 3 additional cases from the families of 3 of the children with epiglottitis (see below).

Many more than 31 children with proved *H. influenzae* type b infections were admitted to the hospitals in question during the relevant years. However, in some cases family studies were impracticable; in some cases (notably when the affected child had died) it was not thought right to suggest investigations which might add to the distress of the family; and in no case were investigations carried out unless the parents agreed readily.

### *The secondary cases*

These have all been previously reported by Addy, Ellis & Turk (1972) and further details can be found in that report. In each case there were only 2 children in the family, and the older of them had been admitted to hospital with epiglottitis. In the first of these families (E 3 in Table 4) the 2-year-old girl developed epiglottitis 3 weeks after her 3-year-old sister: of the 31 children described above as having 'proved *H. influenzae* type b infection' she was the only one from whom that organism was not isolated (probably because she had chloramphenicol before admission to hospital), but it had been isolated from her sister 3 weeks earlier. In another family (E 6 in Table 4) the 11-month-old boy developed typical haemophilus cellulitis of the face 2 days after his older brother had been admitted with epiglottitis. In a third family (E 7 in Table 4) the 1-year-old boy was admitted with suspected epiglottitis 2 months after his older brother had had that disease; in fact, the younger boy had typical follicular tonsillitis, and there was nothing visibly wrong with his epiglottis, but his blood culture grew *H. influenzae* type b.

### *The composition of the families*

Data about the sexes, ages and family situations of the children who had meningitis or epiglottitis are summarized in Tables 1 and 2. The main differences between these two groups were as follows:

(1) The majority of the children with meningitis and the majority of their siblings

Table 1. *Numbers and sexes of the patients with meningitis or epiglottitis and their siblings*

| | Number of patients | | | | Number of siblings | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Male | Female | M/F ratio | Total | Per patient | Male | Female | M/F ratio |
| Meningitis | 14 | 6 | 8 | 0·75 | 33 | 2·35 | 13 | 20 | 0·65 |
| Epiglottitis | 11* | 8 | 3 | 2·66 | 18 | 1·64 | 14 | 4 | 3·50 |

* In one family both children (girls of 3 years and 2 years) developed epiglottitis, with an interval of 3 weeks between them. For purposes of Tables 1 and 2 they have been counted as two patients with epiglottitis, each of whom had one sister.

Table 2. *Ages and positions in families of the patients with meningitis or epiglottitis*

| | Number of patients aged (in years) | | | | Number of patients with siblings as follows: | | | |
|---|---|---|---|---|---|---|---|---|
| | < 1 | 1 | 2 | 3 | None | None younger, 1 older | None younger, 2 or more older | 1 younger, none older |
| Meningitis | 6 | 7 | 0 | 1 | 2 | 4 | 7 | 1 |
| Epiglottitis | 0 | 5 | 3 | 3 | 1 | 2 | 4 | 4 |

were female; whereas there was a marked predominance of males among the children with epiglottitis and among their siblings.

(2) The families of the children with meningitis were on average larger than those of the children with epiglottitis.

(3) Only one of the 14 children with meningitis was over 2 years old, and he was the only one of them who had a younger sibling; whereas 6 of the 11 children with epiglottitis were over 2 years old, and 4 of these 6 had a younger sibling each.

(4) A slightly higher proportion of the children with meningitis than of those with epiglottitis had 2 or more older siblings (7 of 14 as against 4 of 11). These figures are unaffected by exclusion of siblings over 10 years old.

The composition of the families of the 3 children with arthritis and the one with conjunctivitis is shown in Table 4 (A 1–3 and C).

## METHODS OF INVESTIGATION

### *Specimens*

Ideally, within 4 days of the admission of the affected child to hospital a per-nasal swab, a throat swab and a venous blood sample were collected from each parent and from each sibling resident in the home. In a few cases the family were not investigated until the second child was admitted to hospital (see below). Sometimes, when clinical colleagues kindly collected swabs for me, they took only throat swabs or took nasal swabs that probably did not reach the nasopharynx.

Table 3. *Results of initial investigations of families of patients with meningitis*

| Family | Sex and age of patient | Brothers | | | | Sisters | | | | Parents | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M 1 | Male | 3 | . | . | . | . | . | . | . | Mo* | Fa* |
| | 1 year | 64 | . | . | . | . | . | . | . | — | — |
| M 2 | Female | . | . | . | . | . | . | . | . | Mo | Fa |
| | 1½ years | . | . | . | . | . | . | . | . | — | — |
| M 7 | Female | ? | . | . | . | . | . | . | . | Mo | Fa |
| | 9 months | — | . | . | . | . | . | . | . | — | 32 |
| M 10 | Male | . | . | . | . | . | . | . | . | Mo | Fa |
| | 1½ years | . | . | . | . | . | . | . | . | — | — |
| M 11 | Male | . | . | . | . | (3) | . | . | . | Mo | Fa |
| | 7 months | . | . | . | . | . | . | . | . | — | — |
| M 13 | Male | . | . | . | . | 1 | . | . | . | Mo | Fa |
| | 3 years | . | . | . | . | n.t. | . | . | . | — | — |
| M 14 | Female | . | . | . | . | 3 | . | . | . | Mo | Fa |
| | 6 months | . | . | . | . | n.t. | . | . | . | — | — |
| M 3 | Female | 8* | 12 | 15 | 17 | 4 | 10* | 18 | 21 | Mo | Fa |
| | 1½ years | 128 | — | — | — | — | 32 | — | — | — | — |
| M 4 | Male | 3 | . | . | . | 2 | . | . | . | Mo* | Fa |
| | 7 months | 32 | . | . | . | 128 | . | . | . | 64 | 16 |
| M 5 | Male | . | . | . | . | 3* | 5 | 11 | 15 | Mo | Fa |
| | 1¼ years | . | . | . | . | n.t. | 256 | — | — | — | — |
| M 6 | Female | 3 | . | . | . | 1* | 4 | . | . | Mo | Fa |
| | 9 weeks | n.t. | . | . | . | n.t. | 32 | . | . | 32 | 16 |
| M 8 | Female | 2* | 5* | 7 | . | 2* | (18) | . | . | Mo | |
| | 5 months | n.t. | 64 | n.t. | . | n.t. | . | . | . | — | |
| M 9 | Female | 4 | 6* | . | . | . | . | . | . | Mo | Fa |
| | 1¾ years | n.t. | 32 | . | . | . | . | . | . | 16 | — |
| M 12 | Female | . | . | . | . | 7 | 9* | 11 | 13 | Mo | Fa |
| | 1¾ years | . | . | . | . | n.t. | 64 | — | — | — | — |

The families are numbered according to the order in which they were investigated, but have been arranged in the table so as to show first the smaller and then the larger families (see text, p. 321).

Numbers in the upper line for each family indicate the ages of the siblings, in years. The age of the brother in family M 7 was not recorded, but was less than 5 years. Parentheses around age figures indicate that no specimens were obtained from these siblings. * indicates that *H. influenzae* type b was isolated from swabs.

Numbers on the lower line for each family indicate antibody titres for *H. influenzae* type b. n.t. = not tested. − = less than 16.

All 28 mothers were investigated, but only 26 of the fathers were available. Collection of samples from siblings was incomplete because some siblings were not available and others would not allow some or all of the investigations; and also because venepuncture was not attempted when it looked likely to be difficult and was on a few occasions attempted without success. From three of the families no blood samples were collected. Swabs and blood samples were in some cases obtained

Table 4. *Results of initial investigations of families of the patients with epiglottitis, suppurative arthritis or conjunctivitis*

| Family | Sex and age of patient | Brothers | | | | Sisters | | Parents | |
|---|---|---|---|---|---|---|---|---|---|
| E 1 | Male | 2 | . | . | . | . | . | Mo | Fa |
| | 3½ years | n.t. | . | . | . | . | . | 32 | — |
| E 3† | Female | . | . | . | . | . | . | Mo | Fa |
| | 3 years | . | . | . | . | . | . | — | — |
| | Female | . | . | . | . | . | . | | |
| | 2 years | . | . | . | . | . | . | | |
| E 4 | Male | . | . | . | . | . | . | Mo | Fa |
| | 1½ years | . | . | . | . | . | . | — | 32 |
| E 6 | Male | 11/12* | . | . | . | . | . | Mo* | Fa |
| | 2½ years | — | . | . | . | . | . | — | — |
| E 7 | Male | 1 | . | . | . | . | . | Mo | Fa |
| | 3½ years | — | . | . | . | . | . | — | — |
| E 9 | Male | 3* | . | . | . | . | . | Mo | Fa |
| | 1½ years | 32 | . | . | . | . | . | — | — |
| E 2 | Male | 5 | 7 | . | . | . | . | Mo | Fa |
| | 2 years | n.t. | n.t. | . | . | . | . | 16 | 32 |
| E 5 | Male | (5) | (7) | 9 | . | . | . | Mo | Fa* |
| | 1¾ years | . | . | n.t. | . | . | . | n.t. | n.t. |
| E 8 | Male | 6 | 6 | 8 | 11 | 10 | . | Mo | Fa |
| | 1½ years | — | — | — | — | 64 | . | — | — |
| E 10 | Female | 6 | . | . | . | 8 | . | Mo | Fa |
| | 1½ years | 32 | . | . | . | — | . | — | — |
| A 1 | Female | . | . | . | . | 3 | . | Mo | . |
| | 2 years | . | . | . | . | n.t. | . | n.t. | . |
| A 2 | Male | . | . | . | . | . | . | Mo* | Fa |
| | 11 months | . | . | . | . | . | . | 256 | — |
| A 3 | Male | . | . | . | . | 1 | 6 | Mo | Fa |
| | 5 months | . | . | . | . | n.t | n.t. | n.t. | n.t. |
| C | Male | 4* | 6* | . | . | . | . | Mo | Fa |
| | 9 months | — | 64 | . | . | . | . | — | — |

† Family E 3 were not investigated at the time of admission of the older child. The parents were investigated 3 weeks later, when the younger child was admitted.

For the interpretation of other symbols and the numbers in this table, see footnotes to Table 3.

from close contacts other than the parents or siblings, usually with negative results which are not included in this report; but in one household there were some positive findings, which are included in the text but not in the tables.

From 10 of the 28 families further specimens were collected on one or more occasions after the initial investigations, the longest follow-up period being 10 months.

*Laboratory procedures*

Swabs were plated out (in most cases within 2 hr. of collection) on 'chocolate' agar and on blood agar to which a streak of *Staphylococcus aureus* was added, as previously described (Turk, 1963). Capsulated strains of *H. influenzae* were identified by iridescent growth on Levinthal agar and were typed by agglutination and capsule-swelling tests with type-specific antisera obtained from Hyland Laboratories, Los Angeles; the techniques were as described by Turk & May (1967).

Antibodies to the capsular antigen of *H. influenzae* type b were detected and measured in the blood samples by the indirect (passive) haemagglutination method of Turk & Green (1964), who suggested that a titre of 32 for this serotype should be regarded as abnormally high or 'positive'. Since then I have applied this method to blood samples from many hundreds of blood donors and of adult hospital patients in whom there was no reason to suspect recent infection with *H. influenzae* type b. The proportion giving titres of 32 or more has varied from 6–8 % of blood donors and patients in London, Newcastle and an industrial area of Scotland to 1–3 % of blood donors from rural areas of England and of Oxford hospital patients. It has not been possible to obtain comparable data about healthy children, but of 50 children aged 4–9 years admitted to hospital in Newcastle for conditions unlikely to be due to haemophilus infection, 5 (10 %) gave titres of 32. In contrast, I have records of 28 patients or healthy subjects aged between 2 and 82 years (not including any of those in the survey described in this paper) from whom *H. influenzae* type b was isolated and blood samples were available, and 21 of these were found to have titres for *H. influenzae* type b between 32 and 128. Furthermore, each of the 7 exceptions was an adult whose only blood sample was collected within less than a week of isolation of the *H. influenzae* and of the onset of an acute illness (meningitis or chest infection) for which that organism was presumably responsible. In the light of all these findings (not previously published), titres of 32 or more for *H. influenzae* type b by this method can be regarded as usually reflecting experience of that organism.

## RESULTS OF INITIAL INVESTIGATIONS

The results of investigations carried out in each of the 28 families within a few days of the admission to hospital of the index case are shown in Tables 3 and 4 and analysed in Table 5. Throughout this and subsequent sections the following abbreviations will be used: *carrier*, to mean someone shown by swabbing to be carrying *H. influenzae* type b; *raised antibody titre*, to mean a haemagglutination titre of 32 or more: *smaller family*, to mean one in which the patient was an only child or had only one sibling; and *larger family*, to mean one containing at least 3 children.

*Findings in the families of patients with meningitis*

In only 2 of the 7 smaller families were there any positive findings; in one of these both parents were carriers and the one sibling (3 years old) had a raised antibody titre, and in the other the father had a raised antibody titre. Three of the

5 smaller families with no positive findings each contained one child other than the patient; one of these 3 was not investigated, and no blood samples were obtained from the other 2. There were 2 single-child families with negative findings from the parents; however, when unrelated people living in the same house as one of these families (M 2 in Table 3) were investigated a 4-year-old girl was found to be a carrier and an adult female was found to have raised antibody titre.

Each of the 7 larger families was found to contain at least one carrier and at least one member with a raised antibody titre. Nine of the 10 carriers and 9 of the 11 members with raised antibody titres were children aged 1–10 years; 14 of the 18 siblings in this age-group gave positive results by one means or the other, and all 4 exceptions were children whose blood was not examined. One of the 7 mothers was found to be a carrier, and she and one other mother had raised antibody titres. All 9 siblings aged 11 years or over and all 6 available fathers were examined, by swabbing and serologically, with negative results.

Altogether, 10 of the 14 meningitis patients were found to have household contacts who had raised antibody titres, and carriers were found in 9 of these 10 households. Three of the remaining 4 patients had siblings whose antibody status was not determined.

*Findings in the families of patients with epiglottitis*

Four of the 6 smaller families gave positive findings; in one a younger (11-month-old) sibling and the mother were found to be carriers, in one a 3-year-old sibling was found to be a carrier and to have a raised antibody titre, and in the other 2 the mother and father respectively had raised antibody titres. In family E 3 (Table 4) the 'initial' investigations of the parents were negative, but these were not carried out until the second child had been admitted to hospital with epiglottitis; she had a titre of 32 for *H. influenzae* type b at the time of her admission, and that serotype had been isolated from her sister's upper respiratory tract and blood 3 weeks earlier. In the remaining small family, swabs and blood samples from both parents and the one sibling gave negative results.

Only one carrier (a father) was found in the 4 larger families; no blood samples were obtained from that family, and no swabs from 2 of the siblings. Each of the 3 remaining larger families was found to contain one member with a raised antibody titre (a father, a 10-year-old sibling and a 6-year-old sibling). In contrast to the findings in the larger families in the meningitis series, no carriers were found among the 9 siblings in the 0–10 years age-group who were swabbed, and only 2 out of the 6 of them from whom blood samples were obtained had raised antibody titres.

Altogether, 6 of the epiglottitis patients (out of 11 in 10 families) were found to have family contacts who had raised antibody titres; in only one of these 6 families was a carrier found. The remaining 4 families were the one from which no blood samples were obtained and the 3 two-child families in each of which the second child also developed an illness attributable to *H. influenzae* type b.

*Findings in the families of patients with other diseases*

No carriers were found in the families of 2 of the children with suppurative arthritis, and no blood samples were obtained from these 2 families. The mother of the third child with arthritis (an only child) was shown to be a carrier and had a high antibody titre (256). Both brothers (aged 4 and 6 years) of the child with conjunctivitis and probable orbital cellulitis were found to be carriers, and one of them had a raised antibody titre.

*Combined results from the 28 families*

Carriers of *H. influenzae* type b were found in 13 of the 28 families (4 of 15 smaller families and 9 of 13 larger families) and among the household contacts of one other (smaller) family.

Members with raised antibody titres were found in 17 of the 25 families from which any blood samples were obtained (6 of the 14 smaller families and all 11 larger families) and among the household contacts of one other (smaller) family. Three more of the smaller families each contained one sibling from whom no blood was obtained. In one family (M 10), in which the only child had meningitis, swabs and blood samples from both parents gave negative results. There remain the 3 families in each of which both children had illnesses attributable to *H. influenzae* type b and both parents gave negative results from swabs and blood samples.

## RESULTS OF SUBSEQUENT INVESTIGATIONS

It was possible to obtain specimens on one to three further occasions, at times varying from 2 weeks to 10 months after the initial investigations, from members of 10 of the 28 families. The families investigated and the timing of the investigations are indicated in Table 6, but for simplicity only those siblings and parents who at some time gave positive results are listed in the table.

Of the 48 siblings and parents who were repeatedly investigated, 27 (6 siblings under 11 years old, 7 older siblings and 14 parents) always gave negative results. Five of them were swabbed 4 times (including the initial investigations), 3 of them 3 times and the other 19 twice. From 3 of them there were no initial blood samples, but one of these had a sample taken 6 weeks later. From 9 others only initial blood samples were tested, but from the remaining 15 subjects a total of 40 samples (15 initial and 25 subsequent) were examined.

The findings from the other 16 siblings (14 of them under 11 years old) and 5 parents are shown in Table 6. These 21 subjects can be classified as follows:

(*a*) *Six who were initially found to be carriers and to have raised antibody titres.* Five were again found to be carriers on subsequent examinations, after intervals of 3 months in two cases, but the sixth was not re-examined for 4 months and at that stage her swabs gave negative results. The 3 whose antibody measurements were repeated continued to have raised titres.

(*b*) *Two who were initially found to be carriers, but without raised antibody titres.* One, who was not shown subsequently to be a carrier, developed an antibody titre

Table 5. *Analysis of results shown in Tables 3 and 4*

| Diagnosis of index case | Proportions of appropriately investigated family members who were found to be carriers of *H. influenzae* type b (C columns) or to have antibody titres of 32 or more for that serotype (T columns) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Siblings 0–10 years | | Siblings 11 years or more | | Mothers | | Fathers | |
| | C | T | C | T | C | T | C | T |
| Meningitis | | | | | | | | |
| 7 smaller families | 0/4 | 1/2 | | | 1/7 | 0/7 | 1/7 | 1/7 |
| 7 larger families | 9/18 | 9/10 | 0/9 | 0/9 | 1/7 | 2/7 | 0/6 | 0/6 |
| Epiglottitis | | | | | | | | |
| 6 smaller families | 2/4 | 1/3 | | | 1/6 | 1/6 | 0/6 | 1/6 |
| 4 larger families | 0/9 | 2/6 | 0/1 | 0/1 | 0/4 | 0/3 | 1/4 | 1/3 |
| Others | 2/5 | 1/2 | | | 1/4 | 1/2 | 0/3 | 0/2 |
| Totals | 13/40 | 14/23 | 0/10 | 0/10 | 4/28 | 4/25 | 2/26 | 3/24 |

Table 6. *Results from the 21 siblings or parents who were repeatedly investigated and who gave positive findings on one or more occasions*

| Family | Subject (age in years) | Initial findings | Subsequent findings after intervals of approximately: 2 weeks | 4 weeks | 6 weeks | 2 months | 3 months | 4 months | 6 months | 10 months |
|---|---|---|---|---|---|---|---|---|---|---|
| M 1 | Brother (3) | −64 | . | −64 | . | . | . | . | . | . |
| | Mother | +— | −16 | −16 | −32 | . | . | . | . | . |
| M 3 | Sister (4) | −— | −16 | . | . | . | +n.t. | . | . | −n.t. |
| | Brother (8) | +128 | +128 | . | . | . | −32 | . | . | −32 |
| | Sister (10) | +32 | +64 | . | . | . | +32 | . | . | −16 |
| | Brother (12) | −— | −— | . | . | . | −— | . | . | −128 |
| M 4 | Sister (2) | −128 | . | . | +128 | . | −n.t. | . | −n.t. | . |
| | Brother (3) | −32 | . | . | −n.t. | . | −n.t. | . | −n.t. | . |
| | Mother | +64 | . | . | +64 | . | +64 | . | −32 | . |
| M 5 | Sister (3) | +n.t. | . | . | +n.t. | . | . | . | . | . |
| | Sister (5) | −256 | . | . | −64 | . | . | . | . | . |
| M 12 | Sister (7) | −— | . | . | . | . | . | +n.t. | . | . |
| | Sister (9) | +64 | . | . | . | . | . | −n.t. | . | . |
| | Sister (13) | −— | . | . | . | . | . | +n.t. | . | . |
| E 1 | Mother | −32 | . | . | . | . | . | −32 | . | . |
| E 2 | Father | −32 | . | . | −16 | . | . | . | . | . |
| E 8 | Sister (10) | −64 | . | . | . | +64 | . | . | . | . |
| | Mother | −— | . | . | . | −128 | . | . | . | . |
| E 9 | Brother (3) | +32 | . | . | . | +n.t. | . | . | . | . |
| C | Brother (4) | +— | . | . | +n.t. | . | −n.t. | . | . | . |
| | Brother (6) | +64 | . | . | +n.t. | . | −n.t. | . | . | |

Each entry in this table begins with + or − to indicate whether *H. influenzae* type b was grown from swabs, followed by the antibody titre recorded as in Table 3.

of 32. The other was still a carrier after 6 weeks, but had negative swab results after 3 months; no blood was collected from him on either of these occasions.

(*c*) *One who was a carrier initially and* 6 *weeks later, but had no serological tests.*

(*d*) *Seven who had raised antibody titres initially but were not at that time found to be carriers.* Three of these were found to be carriers subsequently, and it seems likely that their initial 'non-carrier' status reflected the unreliability of swabbing as a means of detecting carriers. Of the 6 who had repeated antibody measurements, 5 had persistent titres of 32 or more, and in the sixth case the initial reading was 32 and the only subsequent reading, 6 weeks later, was 16.

(*e*) *Five whose initial swabs and blood samples gave negative results.* Of these, 3 were subsequently found to be carriers but no blood samples were collected from them at that stage or subsequently. Carriage by the other 2 was not demonstrated by swabbing, but both developed antibody titres of 128.

During the course of the repeated investigations of the 10 families, upper respiratory tract swabs were collected on one or more occasions from the original patient in each family. *H. influenzae* type b was isolated from those in families M 3 (at 3 months after admission), M 4 (at 6 weeks and at 3 months), M 12 (at 4 months), E 2 (at 6 weeks) and E 9 (at 2 months). Blood samples were collected from 2 of these 10 patients (the boy in family M 1 at 2, 4 and 6 weeks, and the girl in family M 12 at 4 months) and from 2 other children whose families were not re-investigated (the girl in family M 2 at 3 months and the boy in family M 11 at 1 month) that from the girl in family M 12 had a titre of 16, and the other samples all had titres of less than 8.

## DISCUSSION

The number of families investigated was small and, selected as they were, they may not have been truly representative of all families in which these acute haemophilus infections occur. In this discussion the findings are first reviewed in the light of previous publications, and then some interpretations and an application of the findings are suggested.

### *Sex ratio*

Many series of cases of haemophilus meningitis have shown a predominance of males among the patients, of about 3:2 or 5:4, as reported by Lindsay, Rice & Selinger (1940), Koch & Carson (1955), Shaw & Bruyn (1960) and Thrupp *et al.* (1964), all from the U.S.A., and Turk & Wynter (1961) from Jamaica. Smaller sex differences were reported by Ouyang & Ting (1957) from Shanghai and by Barrett and his colleagues (1972) from Texas; and even a female predominance (36:43) by McGowan and his colleagues (1974) from Massachusetts. From Britain, Bevan-Jones & Miller (1967) reported a male predominance, but did not make clear its size (except that it was substantially less than 3:2) or the proportion of their 243 patients who were children and of known sex. Of 59 children with haemophilus meningitis admitted to English hospitals (mostly in Newcastle or Oxford) from whom I received strains of *H. influenzae* type b between November 1961 and January 1975, and whose sex I know, 33 were boys and 26 were girls–again a ratio of about 5:4. As the 14 children with meningitis referred to in the

present paper were included in the 59, the predominance of girls among the 14 was clearly a misleading effect of small numbers.

For epiglottitis there is also clear evidence of a predominance of males as reported by Rabe (1948), Berenberg & Kevy (1958), Milko, Marshak & Striker (1974) and Bass, Steele & Wiebe (1974) from the U.S.A., Baxter (1967) from Montreal and Jones & Camps (1957) and Jones (1970) from England, but in most of these series the predominance was greater than in haemophilus meningitis – of the order of 2:1 or 5:3. My own figures, collected in much the same way as those for meningitis given in the previous paragraph, are that of 26 children with epiglottitis (including the 11 referred to in the present paper) 16 were boys and 10 were girls – a ratio in keeping with other published series. Sex as a factor influencing liability to disease is clearly more important in epiglottitis than in haemophilus meningitis, though not to the extent suggested by the ratios given in Table 1.

The effect of the sex of siblings in determining the incidence of these two diseases has not, so far as I know, been investigated previously. The difference in sex ratio found in the present study – 13 brothers and 20 sisters in the meningitis families as against 14 brothers and 4 sisters in the epiglottitis families – is statistically significant ($P$ just less than 0·02) and calls for further investigation.

*Number of siblings*

The observation by Ounsted (1950) quoted in the introduction to this paper was made in Oxford and confirmed by additional data from Oxford and Leeds and from Copenhagen (Ounsted, 1951). In his 1951 calculations Ounsted included all siblings under 14 years old, and showed that 23 (67·6 %) of 32 children with haemophilus meningitis in Oxford and Leeds had two or more such siblings, as compared with only 26 % of control children in Oxford. Family sizes were smaller in Copenhagen at that time: only 11·3 % of a very large series of control children had two or more siblings under 14 years old, whereas the figure for children with haemophilus meningitis was 28 % (12 of 43). Ounsted noted that many young children in Copenhagen were exposed to contact with children other than their siblings because they attended day-nurseries. Since Ounsted's English figures were collected in post-war years, when the birth-rate in this country was higher than it has been in recent years, the finding in the present series that 7 (50 %) of the 14 children with meningitis had two or more siblings under 12 years old suggests that family size is still an important determinant of the incidence of this disease. The corresponding figures for the children with epiglottitis – 4 (36 %) of 11 – point somewhat less firmly in the same direction; and the average number of siblings per patient was lower for those with epiglottitis (1·64) than for those with meningitis (2·35).

*Ages and family positions of patients*

Ever since the first report of a series of cases of epiglottitis (under the name 'acute laryngitis with bacteraemia') by Sinclair in 1941, it has been clear that children affected by this disease are usually older than the majority of those with haemophilus meningitis. Some 40–50 % of cases of haemophilus meningitis occur

in the first year of life, and 60–80% within the first 2 years (see, for example, Koch & Carson, 1955; Thrupp *et al.* 1964; Parke, Schneerson & Robbins, 1972), whereas epiglottitis is predominantly a disease of children between the ages of 2 and 4 years, and is uncommon in the first year of life (Jones & Camps, 1957; Baxter, 1967; Jones, 1970; Milko *et al.* 1974). The patients with these two diseases in the present series conform to these age-patterns.

The fact that haemophilus meningitis usually affects the youngest member of a family, whereas epiglottitis patients may have younger siblings, is merely another expression of the difference in age-incidence. In the present series, the 5 patients (1 with meningitis and 4 with epiglottitis) who each had a younger sibling were also the only patients aged $2\frac{1}{2}$ years or more.

*Results of investigations of family members*

The high frequency of carriers of *H. influenzae* type b in the households of children with acute illnesses caused by that organism was first demonstrated by Good and his colleagues (1943), as mentioned earlier, and was confirmed, in relation to haemophilus meningitis in Jamaica, by Turk (1962, 1963). There is little other published work on this subject.

Isolation of *H. influenzae* type b from a nasopharyngeal swab is unequivocal evidence that the person swabbed was carrying that organism at the appropriate time. A negative result, however, may mean either that he was not carrying it or that the procedure failed to detect its presence. The consistency with which initial negative or positive swab results in the present investigation were reproduced on subsequent occasions suggests that the swabbing and culturing techniques were in general reasonably reliable, though it does not exclude the possibility that carriage of a small population of *H. influenzae* type b may have been repeatedly missed. If the test did in fact substantially underestimate the number of carriers, the one carrier in a small family would be more liable to be missed than the two or more who might be present in a larger family. Such an effect may be at least part of the explanation of my failure to find carriers in 6 of the 7 smaller families in the meningitis series, whereas all 7 of the larger families were found to contain them. However, the total carrier frequencies found among siblings under 11 years old were different for the two sizes of family, though the numbers (0 of 4 as against 9 of 18) are too small for definite significance.

The problems in interpreting antibody titres are different. Unlike swabbing, the serological procedure used is probably not liable to give false negative results; a titre of 32 or more, when present, is reliably detected, as the consistent results from repeated examinations of the same subjects confirm. (A titre of 16 is, of course, more problematical, but there were only a few such, as the tables show.) A positive result, however, is by no means so clear in its meaning as a positive swab result. The presence of antibodies that react with *H. influenzae* type b polysaccharide is not unequivocal evidence of past encounter with that particular organism, as similar antigens have been found in unrelated bacteria (Schneerson *et al.* 1972; Myerowitz, Gordon & Robbins, 1973). Furthermore, titres around 32 may persist for months or years after an encounter with *H. influenzae* type b (Turk & Holda-

way, 1968), though titres of 128 or 256 probably mean that the encounter was recent.

Despite these reservations, the results obtained from the members of the 28 families permit a number of statements and conclusions:

(1) Ounsted (1950) was clearly right to suggest a connexion between family size (and in particular the number of siblings under 12 years old) and the incidence of haemophilus meningitis. In the 28 families as a whole, but outstandingly in the larger families in the meningitis group, siblings aged 0–10 years dominate the picture, both as carriers at the time of the initial investigations and, more importantly, as those whose antibody titres indicated them as possible sources of infection for the patients. Conversely, siblings over 10 years old appeared to play no part in the transmission of the organism to the patients, though two of them gave serological evidence of infection later. It may well be that most children in this latter age-group have met *H. influenzae* type b earlier in life and are protected against it – even against carrying it – by antibodies other than those measured by the haemagglutination procedure (see below). The parents were intermediate between the two age-groups of siblings in their apparent importance as carriers and transmitters.

(2) Ounsted also postulated that the haemophilus needed passage through partially immune family members before it acquired the ability to cause meningitis. While the present findings do not permit any comment on possible enhancement of virulence by passage, they provide serological confirmation that the *H. influenzae* type b had been present in most of the families, including all of the 11 larger families from which blood samples were obtained, for long enough before the initial investigations to induce a raised antibody titre in the blood of at least one member of each family. There is thus a strong probability that most of the patients acquired their infections, from within their families, several weeks after the organisms first reached the families.

(3) There remain a number of patients whose source of infection was probably outside the family. For example, the child in family M 2 was probably directly infected from the unrelated carriers in the household; the first of the two affected children in family E 3 presumably acquired her infection from an outside source; and in family E 6 the mother and both children may well have been infected simultaneously from a common outside contact. Detailed study of the habits, and investigation of the contacts, of these and other families with no apparent internal sources of infection might have been informative, but might also have created problems; the findings among the household contacts of family M 2 were unfortunately disclosed to the parents, and their consequent attitude to those whom they considered 'to blame' for their child's illness led to a feud in the household. Ounsted's comments, noted above, on the possible role of Copenhagen day-nurseries may well be relevant to the contemporary English situation.

(4) Persistence of *H. influenzae* type b for a number of months was demonstrated in several families (Table 6). Its distribution within the families was surprisingly stable, in that few of the family members whose initial results were negative showed evidence of subsequent acquisition. Boisvert (1948) reported persistence of this

organism in families for years, and referred to members passing it back and forth; but without any serological information it is impossible to say whether this apparent interchange was in fact due to erratic detection of persistent carriage by the same individuals.

(5) It is clear from the data in Table 6 that a raised titre of haemagglutinating antibodies is not incompatible with continued carriage of *H. influenzae* type b. Indeed, a titre of 32 did not prevent the second child in family E 3 from developing epiglottitis. Johnston, Anderson, Rosen & Smith (1973) studied the specific haemagglutinating, bactericidal and opsonizing activities of serum from a healthy adult who had been immunized with *H. influenzae* type b polysaccharide (polyribophosphate). They showed that nearly all the haemagglutinating activity of the serum was due to the small IgM component of the specific antibodies, whereas the IgG component supplied most of the bactericidal and all of the opsonizing activity. Thus, while haemagglutinating antibodies are useful to the investigator as evidence of recent exposure to *H. influenzae* type b, they may not have much to do with the patient's resistance to infection by that organism; and it is not to be expected that antibodies of class IgM would affect carriage on mucous surfaces.

*Follow-up of the patients*

Even a recent severe illness due to *H. influenzae* type b does not preclude its subsequent carriage in the nasopharynx, as was shown by the five recovered patients who were carrying it weeks or months after returning home.

The lack of antibody response by the 4 meningitis patients (aged 7 months to $1\frac{1}{2}$ years) from whom blood was collected after their illnesses is in keeping with the finding by Norden, Melish, Overall & Baum (1972) that haemagglutinating or bactericidal antibody responses following haemophilus meningitis were rare in children under the age of 2 years.

*Tentative interpretations of some of the findings*

The child with haemophilus meningitis is usually the youngest member of the family, has not yet or only recently learned to walk, and has an above-average chance of having several older siblings under 11 years old – in particular, of having older sisters, if the implications of this survey are correct. If it can be assumed that older sisters are more attentive to babies than are older brothers, then we have described a child who would be more often exposed than most of his contemporaries to close contact with children in the age-group in which carriage of *H. influenzae* type b is commonest; and it is easy to see why he would be particularly liable to develop an illness due to that organism, though it is not clear why that illness should usually take the form of meningitis.

The child with epiglottitis is usually over 2 years old. So far as the evidence of this survey goes, he is less likely than the meningitis patient to have a sister, but may well have one or more brothers. He can perhaps be regarded as old enough to get around and collect his infection himself, rather than having it brought to him in his cot or play-pen. But why should he develop epiglottitis rather than meningitis? In the previous account of the child in family A 1 (Miller & Turk, 1965) we

suggested that trauma had localized her infection to her interphalangeal joint, and that lowered local resistance might similarly account for other localized manifestations of what would otherwise have been symptomless *H. influenzae* type b bacteraemias. The child with epiglottitis, because he is older than the one with meningitis, is more likely to have been eating hard food that could have scratched his epiglottis. This seems an improbable reason for him to develop epiglottitis, but there are two unconvincing clues that do suggest an association between such trauma and that disease. One is that the mother of one of our epiglottitis patients (family E 9) told me, after her child had been admitted to hospital, of an episode that she had not mentioned earlier; on the day before his admission she had had to turn him head downwards and slap his back to dislodge a piece of peanut bar from his throat. The other even less impressive clue is that the only British report of epiglottitis in adults (Johnstone & Lawy, 1967) came from Grimsby, a major fishing port.

It could be that meningitis and epiglottitis are caused by different strains of *H. influenzae* type b, with differences in transmission that might account for the different age-incidences of the two diseases and perhaps even for the different sex-ratios of both patients and siblings. Improbable though this seems, it is noteworthy that, of the three younger siblings of epiglottitis patients who became ill, none developed meningitis although two of them were under 1 year old.

*A possible application of some of the findings*

Immunization with *H. influenzae* type b capsular polysaccharide as a means of preventing haemophilus meningitis and related diseases has been the subject of much work and many papers in the U.S.A. in the past few years. Antibody responses to such immunization have been encouraging in adults, but less so in children, especially in those under 1 year old (Smith, Peter, Ingram, Harding & Anderson, 1973). These findings again fit in well with reports by Norden *et al.* (1972) and Nordern & Michaels (1973) about the lack of antibody response of young children to natural infection with *H. influenzae* type b. South (1972) suggested that 'the immunologic unresponsiveness of the small child to *Haemophilus influenzae* may be explained by a very late position of the defined antigens of this organism in the hierarchy of the recognition system's development'. If she is right, there may be little hope of achieving active immunity against *H. influenzae* type b in children young enough to be at serious risk of developing haemophilus meningitis. The incidence of serious haemophilus infections in children over 1 year old is probably nowhere high enough to justify a campaign for widespread immunization in this age-group. However, the findings in the present survey suggest a line of thought that may encourage the advocates of immunization against *H. influenzae* type b. If most patients with haemophilus meningitis have acquired their infection from their older siblings, then widespread immunization of 2- and 3-year-old children with *H. influenzae* type b polysaccharide might, in addition to protecting them against their own relatively slight hazards from this organism, prevent or greatly reduce carriage of it in the nasopharynx (if the antibodies induced were appropriate for this purpose) and so prevent their younger siblings from getting haemophilus

meningitis. However, such immunization might merely postpone the common age for carrying *H. influenzae* type b into adolescence or early adult life, so that, for example, a young mother might pass on to her newborn baby the organism itself rather than the passive immunity which, according to Fothergill & Wright (1933), is the reason why haemophilus meningitis is rare in the first few months of life.

I am grateful to many clinical and laboratory colleagues, and above all to the parents and children investigated, for their help in this survey.

## REFERENCES

ADDY, M. G., ELLIS, P. D. M. & TURK, D. C. (1972). Haemophilus epiglottitis: nine recent cases in Oxford. *British Medical Journal* i, 40–2.

ALEXANDER, H. E., ELLIS, C. & LEIDY, G. (1942). Treatment of type-specific *H. influenzae* infections in infancy and childhood. *Journal of Pediatrics* **20**, 673–98.

BARRETT, F. F., TABER, L. H., MORRIS, C. R., STEPHENSON, W. B., CLARK, D. J. & YOW, M. D. (1972). A 12 year review of the antibiotic management of *H. influenzae* meningitis. *Journal of Pediatrics* **81**, 370–7.

BASS, J. W., STEELE, R. W. & WIEBE, R. A. (1974). Acute epiglottitis: a surgical emergency. *Journal of the American Medical Association* **229**, 671–5.

BAXTER, J. D. (1967). Acute epiglottitis in children. *Laryngoscope* **77**, 1358–67.

BENNETT, J. V., MCCORMICK, J. B. & FELDMAN, R. A. (1974). *H. influenzae* meningitis. *Pediatrics* **53**, 951–2.

BERENBERG, W. & KEVY, S. (1958). Acute epiglottitis in childhood. *New England Journal of Medicine* **258**, 870–4.

BEVAN-JONES, H. & MILLER, D. L. (1967). Bacterial meningitis 1962–63. *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* **26**, 22–30.

BOISVERT, P. L. (1948). Familial epidemiology of *H. influenzae*, type b, infections. *American Journal of the Diseases of Children* **75**, 427.

CARTWRIGHT, K. & TURK, D. C. (1974). *H. influenzae* cellulitis. *British Medical Journal* ii, 225.

DAWSON, B. & ZINNEMANN, K. (1952). Incidence and type distribution of capsulated *H. influenzae* strains. *British Medical Journal* i, 740–2.

FOTHERGILL, L. D. & WRIGHT, J. (1933). Influenzal meningitis: relation of age incidence to bactericidal power of blood against causal organism. *Journal of Immunology* **24**, 273–84.

GOOD, P. G., FOUSEK, M. D., GROSSMAN, M. F. & BOISVERT, P. L. (1943). Study of familial spread of *H. influenzae*, type b. *Yale Journal of Biology and Medicine* **15**, 913–18.

JOHNSON, R. D. & FOUSEK, M. D. (1943). A study of the spread of *H. influenzae*, type b. *Journal of Bacteriology* **45**, 197.

JOHNSTON, R. B., ANDERSON, P., ROSEN, F. & SMITH, D. H. (1973). Characterization of human antibody to polyribophosphate, the capsular antigen of *H. influenzae* type b. *Clinical Immunology and Immunopathology* **1**, 234–40.

JOHNSTONE, J. M. & LAWY, H. S. (1967). Acute epiglottitis in adults due to *H. influenzae* type *b*. *Lancet* ii, 134–6.

JONES, H. M. (1970). Acute epiglottitis: a personal study over 20 years. *Proceedings of the Royal Society of Medicine* **63**, 706–12.

JONES, H. M. & CAMPS, F. E. (1957). Acute epiglottitis: supraglottitis. *Practitioner* **178**, 223–9.

KOCH, R. & CARSON, M. J. (1955). Management of *H. influenzae*, type b meningitis. *Journal of Pediatrics* **46**, 18–29.

LINDSAY, J. W., RICE, E. C. & SELINGER, M. A. (1940). Treatment of meningitis due to *H. influenzae* (Pfeiffer's bacillus). *Journal of Pediatrics* **17**, 220–7.

MCGOWAN, J. E., KLEIN, J. O., BRATTON, L., BARNES, M. W. & FINLAND, M. (1974). Meningitis and bacteraemia due to *H. influenzae*: occurrence and mortality at Boston City Hospital in 12 selected years, 1935–72. *Journal of Infectious Diseases* **130**, 119–24.

MASTERS, P. L., BRUMFITT, W., MENDEZ, R. L. & LIKAR, M. (1958). Bacterial flora of the upper respiratory tract in Paddington families, 1952–4. *British Medical Journal* i, 1200–5.

MILKO, D. A., MARSHAK, G. & STRIKER, T. W. (1974). Nasotracheal intubation in the treatment of acute epiglottitis. *Pediatrics* **53**, 674–7.

MILLER, I. A. & TURK, D. C. (1965). *H. influenzae* infection of a finger. *British Medical Journal* i, 1042.

MPAIRWE, Y. (1970). Observations on the nasopharyhgeal carriage of *H. influenzae* type b in children in Kampala, Uganda. *Journal of Hygiene* **68**, 337–41.

MYEROWITZ, R. L., GORDON, R. E. & ROBBINS, J. B. (1973). Polysaccharides of the genus *Bacillus* cross-reactive with the capsular polysaccharides of *D. pneumoniae* type III, *H. influenzae* type b and *N. meningitidis* group A. *Infection and Immunity* **8**, 896–900.

NORDEN, C. W., MELISH, M., OVERALL J. C. & BAUM, J. (1972). Immunologic responses to *H. influenzae* meningitis. *Journal of Pediatrics* **80**, 209–14.

NORDEN, C. W. & MICHAELS, R. (1973). Immunologic response in patients with epiglottitis caused by *H. influenzae* type b. *Journal of Infectious Diseases* **128**, 777–80.

OUNSTED, C. (1950). *H. influenzae* meningitis: a possible ecological factor. *Lancet* i, 161–2.

OUNSTED, C. (1951). Ecology of *H. influenzae* meningitis. *Lancet* i, 800.

OUYANG, H. M. & TING, T. T. (1957). *H. influenzae* meningitis. *Chinese Medical Journal* **75**, 908–16.

PARKE, J. C., SCHNEERSON, R. & ROBBINS J. C. (1972). The attack rate, age incidence, racial distribution and case fatality rate of *H. influenzae* type b meningitis in Mecklenburg County, North Carolina. *Journal of Pediatrics* **50**, 765–9.

PITTMAN, M. (1931). Variation and type specificity in the bacterial species *H. influenzae*. *Journal of Experimental Medicine* **53**, 471–92.

RABE, E. F. (1948). Infectious croup III. *H. influenzae* type b croup. *Pediatrics* **2**, 559–66.

SCHNEERSON, R., BRADSHAW, M., WHISNANT, J. K., MYEROWITZ, R. L., PARKE, J. C. & ROBBINS, J. C. (1972). An *E. coli* antigen cross-reactive with the capsular polysaccharide of *H. influenzae* type b. *Journal of Immunology* **108**, 1551–62.

SELL, S. H. W. (1970). The clinical importance of *H. influenzae* infections in children. *Pediatric Clinics of North America* **17**, 415–26.

SELL, S. H. W., TURNER, D. J. & FELDERSPIEL, C. F. (1973). Natural infections with *H. influenzae* in children. In *Hemophilus influenzae* (ed. S. H. W. Sell and D. T. Carson), chap. 1, pp. 3–12. Nashville, Tennessee: Vanderbilt University Press.

SHAW, E. B. & BRUYN, H. B. (1960). Streptomycin in therapy of *H. influenzae* meningitis. *Journal of Pediatrics* **56**, 253–8.

SINCLAIR, S. E. (1941). *H. influenzae* type b in acute laryngitis with bacteraemia. *Journal of the American Medical Association* **117**, 170–3.

SMITH, D. H., INGRAM, D. L., SMITH, A. L., GILLES, F. & BRESNAN, M. J. (1973). Bacterial meningitis: a symposium. *Pediatrics* **52**, 586–600.

SMITH, D. H., PETER, G., INGRAM, D. L., HARDING, A. L. & ANDERSON, P. (1973). Responses of children immunized with the capsular polysaccharide of *H. influenzae* type b. *Pediatrics* **52**, 637–44.

SOUTH, M. A. (1972). Lack of immune response to *H. influenzae*: immune paralysis or immaturity? *Journal of Pediatrics* **80**, 348–50.

THRUPP, L. D., LEEDOM, J. M., IVLER, D., WEHRLE, P. F., BROWN, J. F., MATHIES, A. W. & PORTNOY, B. (1964). *H. influenzae* meningitis: a controlled study of treatment with ampicillin. *Postgraduate Medical Journal* **40** (suppl.), 119–25.

TURK, D. C. (1962). *Haemophilus influenzae in Jamaica*. D.M. Dissertation, University of Oxford.

TURK, D. C. (1963). Nasopharyngeal carriage of *H. influenzae*. *Journal of Hygiene* **61**, 247–56.

TURK, D. C. & GREEN, C. A. (1964). Measurement of antibodies reacting with capsular antigens of *H. influenzae*. *Journal of Clinical Pathology* **17**, 294–6.

TURK, D. C. & HOLDAWAY, M. D. (1968). Capsulated *H. influenzae* and bronchiectasis. *Journal of Medical Microbiology* **1**, 79–88.

TURK, D. C. & MAY, J. R. (1967). *Haemophilus influenzae: Its Clinical Importance*. London: English Universities Press.

TURK, D. C. & WYNTER, H. H. (1961). Meningitis in Jamaica. *West Indian Medical Journal* **10**, 118–31.