Acute respiratory infections in the population[1]

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'... an obvious example, and one that we have all experienced and shall continue to do so, is that of the common cold ...' (Hippocrates)

Introduction

Acute respiratory infections impose a heavy burden of morbidity – heavy because although most individual illnesses are mild, in total they affect a large proportion of the population each year. In a lifetime the individual will probably have from 100 to 200 of these infections (Dingle *et al.* 1964). They may be severe, especially in the very young, the old and those whose health is already compromised by other conditions (Cockburn 1979, Chretien *et al.* 1984) and they may initiate changes early in life which lead to chronic respiratory disease (Reid 1969, Holland 1982).

Although much has been learned about the aetiology of these infections during the past 30 years, there is a sizeable proportion with an as yet unknown cause. Until recently, specific treatment has been available only for some respiratory infections due to bacteria or mycoplasmae. However, interferon and drugs aimed specifically at certain viruses, such as amantadine, idoxuridine and acyclovir, have recently changed the picture and it is likely that more antivirals will soon be available. Vaccine protection for respiratory infections, at present only available against influenza A and B and pneumococcal infection, is likely to be extended to other organisms. For example, no successful vaccine has yet been produced against respiratory syncytial virus, parainfluenza viruses or *Haemophilus influenzae,* although one may soon be developed against this last organism (Lambert 1980). These substances are not cheap and they should in any case be used with maximum efficiency. To do this, the clinician needs to know much more about the epidemiology and clinical effects of respiratory infections. He 'must be prepared to become increasingly involved with respiratory virology by providing well documented clinical data ...' (Crofton & Douglas 1981).

Since the respiratory tract responds to infection with only a limited range of reactions, specific syndromes related to an infectious agent are difficult or impossible to identify. However, certain discriminatory features may reduce the diagnostic possibilities. At present the clinician is very dependent on the results of tests on respiratory secretions, which are slow, expensive and of limited sensitivity. Recent developments have produced more rapid laboratory diagnoses, but suitable specimens are often difficult to obtain.

In this paper I intend to show that studies of these infections in general practice can achieve some understanding of their nature, both by epidemiological methods and by the clinical study of individual infections of known aetiology, and that we can go some way towards making a diagnosis by clinical examination. I also intend to discuss the evidence for the importance of the segment of acute respiratory infections of unknown aetiology and to indicate possible lines of investigation and management.

Respiratory infections in general practice

The large literature reporting on surveys of respiratory infection has usually concentrated on epidemiological and aetiological features, and it has seldom given very full clinical information. The numerous cases coming under the care of general practitioners provide an

[1]Based on Presidential Address to Section of Epidemiology & Community Medicine, 10 May 1984. Accepted 8 November 1984

0141–0768/85/040282–09/$02.00/0

Table 1. Rates for acute respiratory infections

		No./1000 per annum	Reference
General practice	GP morbidity survey	370	Logan & Cushion 1958
	All infections respiratory tract	328–465	Hope-Simpson & Higgins 1969
	All infections respiratory tract	361	Miller 1973
	GP morbidity survey	409	RCGP/OPCS/DHSS 1979
	Epsom 1952–82	400	Author's practice
Volunteer populations	USPH 1924	2010	Townsend & Sydenstricker 1927
	Baltimore 1928/30	3130	Van Volkenberg & Frost 1933
	Cleveland	5600	Dingle *et al.* 1964
	Cirencester 1954/57	7000	Hope-Simpson & Higgins 1969
	Virus Watch NY	3771	Fox *et al.* 1966

opportunity to rectify this deficiency. A surprisingly constant level of infection has been found in those practices which have published their experiences (Table 1). These results, however, refer to patients actually consulting their general practitioners; the true incidence of infection was of course much higher as many infections were not reported, especially minor ones. Studies of volunteer groups, who reported all illnesses, gave much higher but less consistent figures (Table 1). This may be due to the inclusion of respiratory allergic episodes, difficult to differentiate from infection by a self-reporting group. These figures suggest that between only 1 in 15 and 1 in 20 patients with these infections actually consult a doctor. This underlines the very considerable load of infection in the population.

My own figures were gathered from a group of individuals registered with me as National Health Service patients, for whose care I was personally responsible except during holiday periods. I would thus see and record most of the infections in this group, for which a doctor was consulted. The population resided in a suburban town with a mainly commuter population, the majority belonging to the middle socioeconomic groups. The population register was frequently updated for known accessions and deletions; the total estimated to be at risk at any time was about 10% less than that of the official NHS totals. Nevertheless, the registration of patients with a single practitioner for the provision of general medical services provides the means of defining a population for epidemiological measurement that is not available outside the National Health Service.

The population, which totalled 1198 in 1951, increased gradually to a maximum of 2960 in 1969 and then fell slowly to 2312 by 1983 – the life cycle of an individual practice. Within these totals, the proportion of those aged beween 15 and 64 years remained fairly constant. In contrast, over the same period, the proportion of those up to 4 years of age decreased from 11% to 4%, while that of those aged more than 64 years increased from 6.3% to 22%.

The total number of respiratory infections per 1000 per month were as shown in Figure 1. There were a few gaps where resolve or opportunity failed. The well known but still unexplained seasonal swing was clearly shown, the lowest level being in summer; this was fairly constant from year to year. The high peaks in winter were all associated with influenza epidemics, which accounted for most of the variation of annual rates; when these were absent or slight, the winter level was $2\frac{1}{2}$ to 3 times that of the summer. This regularity, which has been reported in other studies, was remarkable, as so many different pathogens were responsible. There must have been an averaging effect together with a fairly constant threshold of severity of illness prompting consultation.

The diagnostic categories appearing in Figure 2 were those defined in the Public Health Laboratory Service survey, of which some of these records were a part (Miller 1973). The diagnosis was fixed by that part of the respiratory tract which was judged to be most severely involved. Lest you should think this to be a modern classification, consider the scheme of Celsus, a physician of the first century AD: 'dripping from the head, sometimes into the nose,

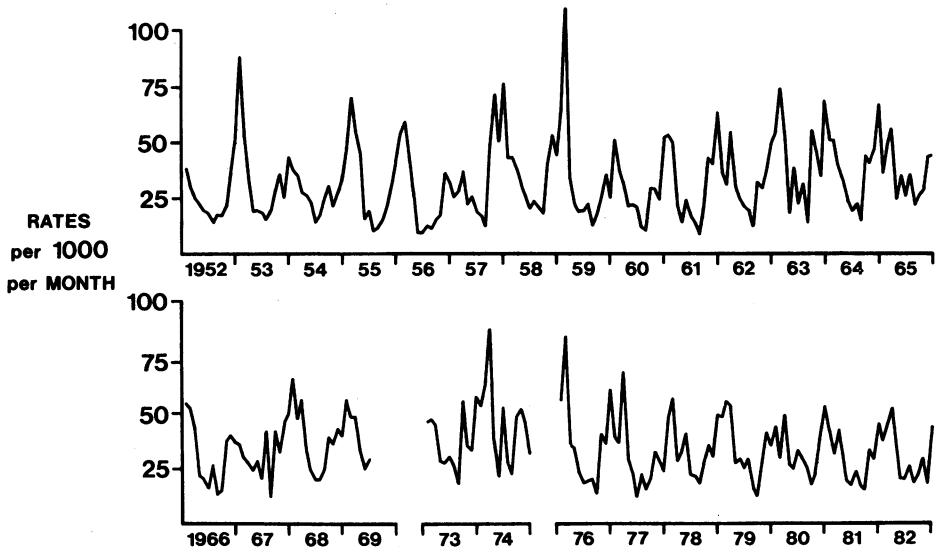

Figure 1. Acute respiratory infections in general practice (available monthly observations, Epsom 1952–82)

which is a mild affair. Sometimes into the throat which is worse, sometimes into the lung, which is worst of all'. Celsus is quite clear in spite of his fanciful pathology, and he also gives the prognosis. The clear distinction between nasal and pharyngeal infections is often blurred in modern reports, and confusion arises by counting them together as upper respiratory infections. There is no confusion here.

Diagnostic groups

The incidence rates of ascertained illness by age and diagnosis were calculated over fifteen annual periods and were similar to those reported in the PHLS survey over one year (Figure 2). This showed the very different behaviour of pharyngitis from other respiratory infections (Miller 1973) as had also been noted by van Volkenberg & Frost (1933). Common cold rates were very high in infancy but fell to a low and steady level in adult life. Assuming an ascertainment rate of 1 in 15, adults had one or two colds per year. Pharyngitis showed the characteristic peak at school age, and then tailed off to a low level in adult life. Perhaps the organisms responsible for these infections were more easily transmitted at school; or they might have caused a different type of illness in infancy. The rates for otitis media are not shown, but their age distribution resembled that of pharyngitis at a very much lower level.

Rates for middle and lower respiratory tract infection were quite different. There was, however, a peak at school age when exposure to adverse climatic conditions and to a variety of infections is high. But there was then a fall in the adult rates, with a further rise in the older age group, as the defences of the respiratory tract weakened.

Thus there is a similarity in the age distributions of common cold and the middle and lower respiratory tract infections, while pharyngitis and otitis media follow a different pattern. The difference between the two groups seemed to have been consistent over a long period.

The seasonal distribution of different clinical syndromes also fell into one of two patterns. Pharyngitis had a spring-summer predominance, while common colds, middle and lower respiratory tract infections had a winter incidence. This was supported by correlations between the numbers of different illnesses occurring in each of the consecutive 4-week periods of the year (Table 2). Common colds and middle and lower respiratory tract infections were significantly associated, as were pharyngitis and otitis media. These distinct seasonal patterns suggest that the two groups of illnesses are caused by different organisms.

In addition to these epidemiological observations in the practice population as a whole, throat and nose swabs were obtained during the period 1962 to 1969 from a sample of

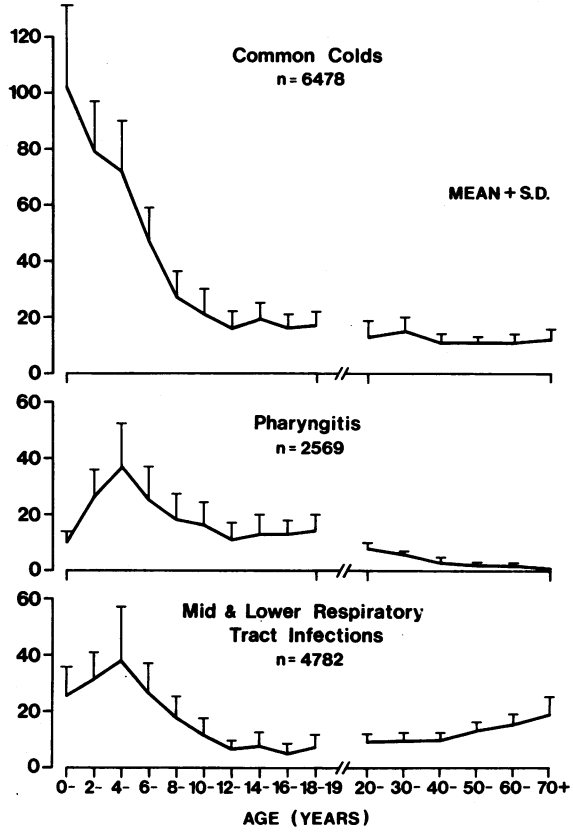

Figure 2. Mean age rates/100 patients/per annum (15 annual periods, Epsom 1962–81)

Table 2. Correlation coefficients between number of cases per 4-weekly period for each diagnosis (Epsom 1962–81)

	Pharyngitis	Middle & lower RTI	Influenza	Otitis media
Common cold	0.160	0.728●	0.346●	0.143
Pharyngitis		0.071	0.020	0.394●
Middle and lower RTI			0.288●	0.121
Influenza				0.072

RTI = respiratory tract infection
● $P < 0.001$ (Student's t test)

patients, using standard methods of transport and of culture for beta-haemolytic Streptococci and a range of respiratory viruses (Poole & Tobin 1973). As representative a sample as possible was taken from individuals with respiratory infections in the first 5 days of the illness and a clinical record was made and a diagnosis recorded before the results of the tests were known. Where possible, two or three clinical examinations were made during this period. The choice of patient was influenced by the consideration that these patients had come to me for treatment and only incidentally to be investigated; a truly random choice of patients was not made.

The results (Table 3) were similar to those obtained by Hope-Simpson & Higgins (1969). A 30% isolation rate is probably as good as can be obtained by routine culture methods. A

Table 3. Percentage isolation rates

	Epsom (1962–69)	Cirencester (1961–66)●
Rhinovirus	4.0	6.2
Parainfluenza	4.3	2.7
Influenza A and B	3.7	4.3
Adenovirus	4.3	2.1
Coxsackie A and B	6.8	2.5
Respiratory syncytial virus	–	1.6
Herpes simplex virus	1.5	3.4
Haemolytic Streptococcus Group A	6.2	6.6
No. of tests	1004	2707
% positive	32	29

●Hope-Simpson & Higgins 1969

figure for respiratory syncytial virus infections is not shown, as suitable cell cultures for this virus were not available. Suckling mouse injections for coxsackie virus isolation were used; hence, perhaps, the high figures for this group. The rhinovirus isolation rates were low – up to 30% has been achieved in a research situation. Again we could not test for coronaviruses although a few paired sera showed the presence of this infection in 1967. *Mycoplasma pneumoniae* infections were also revealed by antibody tests, but we cultured few.

Nearly 13% of all respiratory infections ascertained were tested, but this probably represented less than 1% of all of these infections. Of ascertained common colds, 9% were tested, of pharyngitis 19% and of the remainder 13%.

Clinical response to infection

Were these different agents associated with recognizably different illnesses? To some extent they were, but for each agent there was a fairly wide spread of clinical diagnoses but often with one diagnosis predominating (Table 4). Rhinoviruses, although they also caused lower and middle respiratory tract infections and very much less often pharyngitis, were significantly associated with common colds. Parainfluenza viruses were similarly associated with middle and lower respiratory throat infections, and influenza A and B viruses taken together were associated with the diagnosis of clinical influenza. There were very few pharyngeal illnesses in the whole of this group.

On the other hand, adenoviruses, coxsackie A and B viruses and beta-haemolytic streptococcal infections all had a high and significant association with pharyngitis. Herpes simplex virus infections were also associated with pharyngitis but this did not reach significant levels. These findings suggest that the pharyngeal and catarrhal types of illness were fairly distinctive on the basis of the infecting agent.

Age-specific isolation rates also differed between the groups: there was a significantly high incidence of beta-haemolytic Streptococci, coxsackie A and B viruses and adenoviruses in the age groups 0–14 years; rhinoviruses, parainfluenza viruses and influenza A and B viruses did not show this predominance in younger persons.

The clinical features of illnesses associated with some of these pathogens can be shown by the proportion of patients who exhibit each sign on successive days of their illnesses (Gwaltney *et al.* 1967). These symptom profiles were for groups of patients and do not refer to individual patients in whom responses were more variable. Patients were broadly matched for age. Figure 3 illustrates the response to three very different types of infection: rhinoviruses, influenza A viruses and beta-haemolytic Streptococci. In spite of the disparity in infecting agents, there were many similar features in clinical response. The acute stage in all was

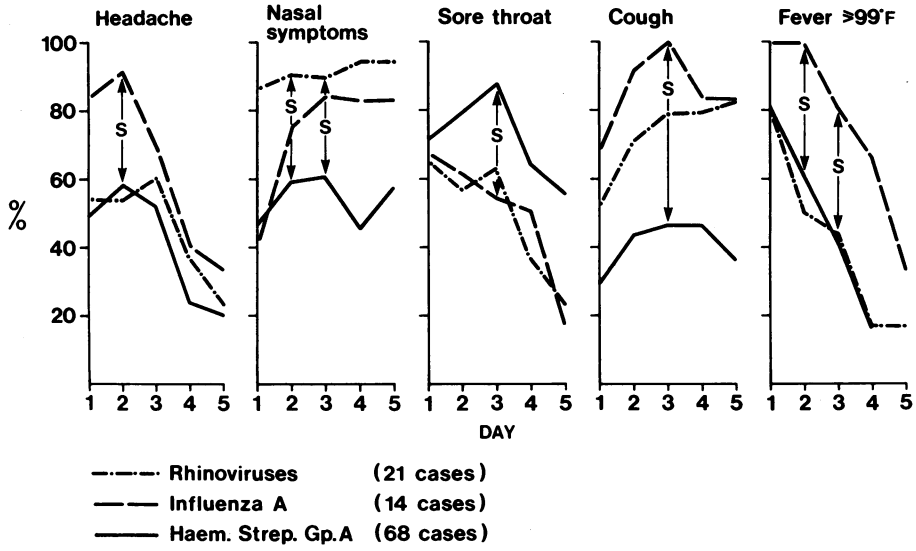

Figure 3. Percentage of cases with given symptoms

short-lived when measured by fever and headache, which virtually disappeared by the fifth day. At onset over 60% in all three types of infection had sore throat, and this may be a source of diagnostic confusion at the start of illness. The patterns for each infection then diverged; sore throat in beta-haemolytic streptococcal infections was significantly more frequent by day three, but nasal symptoms, cough and fever all showed significantly lower levels by that time. Different clinical responses to these three organisms thus developed during the second and third days of illness and allowed clinical differentiation to be made between small groups of patients.

A group of pharyngeal organisms, namely adenoviruses, beta-haemolytic Streptococci and coxsackie A viruses, showed a similar degree of sore throat throughout the illnesses, but adenoviruses caused significantly more headache and fever and more involvement of the nose. The adenoviruses fell midway in their effect between catarrhal and pharyngeal infections. By contrast, there was no significant difference between the clinical response to influenza A and influenzae B infection in age-matched patients (not illustrated).

Detailed day-by-day study of symptoms in groups of patients infected with various organisms is therefore promising as an aid to clinical diagnosis. Indeed, the identity of the causative microorganism in a group of infected patients may be inferred from clinical information alone if the infection is consistently associated with a particular symptom pattern. Infections in which a given symptom was exhibited by 75% or more of individuals during day 2 or 3 of illness are indicated in Table 5. Several group patterns emerge; for example, adenovirus infections were clearly different from influence A virus infections and from beta-haemolytic streptococcal infections. This method of delineating recognizable clinical responses to specific infections together with daily charting of the presence of signs and symptoms would seem to hold out some hope of practical application for the clinician. However, to carry it further, larger groups of patients would have to be studied and the groups would have to be standardized for age, as the clinical response may differ considerably in different age groups.

Special clinical features

Several other clinical features may help in diagnosis. The group of pharyngeal illnesses had a number of characteristic clinical features (Table 6). Follicular exudate, rash and tenderness of the cervical glands were significantly more frequent in beta-haemolytic streptococcal infections compared with illnesses associated with other organisms, or with a group from which no

Table 4. Distribution of diagnoses among positive cases

Agent isolated	Diagnosis				
	Common cold	Pharyngitis	Middle & lower RTI	Otitis media	Influenza
Rhinovirus ($n=40$)	24 (60%)▲	5 (12%)	10 (23%)	0	1 (2%)
Parainfluenza virus ($n=43$)	14 (30%)	7 (16%)	19 (44%)●	2 (5%)	1 (2%)
Influenza A and B viruses ($n=37$)	8 (22%)	1 (3%)	12 (30%)	1 (3%)	15 (40%)▲
Adenovirus ($n=43$)	10 (23%)	22 (51%)■	9 (21%)	0	2 (5%)
Coxsackie A and B viruses ($n=67$)	10 (15%)	40 (59%)▲	13 (19%)	1 (1%)	3 (4%)
Haemolytic Streptococci Group A ($n=62$)	9 (14%)	41 (66%)▲	8 (13%)	2 (3%)	2 (3%)

RTI = respiratory tract infection
Significance by χ^2test: ● $P<0.02$; ■ $P<0.01$; ▲ $P<0.001$

Table 6. Features of pharyngitis (% of patients)

	No pathogens ($n=71$)	Haemolytic Streptococcus Group A ($n=27$)	Adenovirus ($n=18$)	Coxsackie A ($n=18$)	Coxsackie B ($n=13$)	Herpes simplex virus ($n=11$)
Throat exudate	22	58●	33	5●	38	36
Vesicles in throat	11	0	0	39■	8	9
Tender cervical glands	59	78●	33	33	31	51
Rash	0	18■	0	5	0	0

● $P<0.02$–0.01
■ $P<0.001$

Table 5. Infections in which symptom or sign exhibited by 75% or more patients during day 2 or 3 of illness

	Nasal symptoms	Cough	Sore throat	Headache	Fever
Rhinoviruses ($n=21$)	+	+			
Influenza A viruses ($n=14$)	+	+		+	+
Influenza B viruses (n = 21)	+	+			+
Parainfluenza viruses I, II, III ($n=21$)		+			+
Adenoviruses ($n=17$)	+		+	+	+
Coxsackie A viruses ($n=17$)			+		+
Coxsackie B viruses ($n=13$)			+	+	+
Herpes simplex virus ($n=20$)			+	+	+
Haemolytic Streptococcus Group A ($n=68$)			+		

pathogens were isolated. The presence of throat vesicles was significant in coxsackie A virus infections, as was the absence of follicular exudate. During epidemics the clinician should be able to recognize these group patterns. Other syndromes, such as pharyngoconjunctival fever in adenovirus infection, and hand, foot and mouth disease with coxsackie A viruses, are generally easily recognized, as are at least some cases of influenza A or B infection; this is especially important early in an outbreak.

Illness of unknown aetiology

It has for some time been assumed that most of these illnesses are due to viruses. Is this necessarily true?

The position of beta-haemolytic Streptococci is well established, but their activity needs continual monitoring because of their potential to cause severe illness. That of *Strep. pneumoniae* and *Haemophilus influenzae* is more difficult to assess. Both have high carrier rates in respiratory secretions and isolation alone is not necessarily evidence of causation of illness. Some conclusions can be drawn from culture of exudate from the middle ear in otitis media, which yields *Streptococcus pneumoniae* or *Haemophilus influenzae* in about 50% of occasions (Howard *et al.* 1976). It is known that *Strep. pneumoniae* also colonizes the infantile respiratory tract by successive waves of new types and such invasion is often associated with otitis media (Gray *et al.* 1980). The incidence of this infection has been lessened in infants by the administration of pneumococcal vaccine (Lambert 1980). Both these organisms therefore cause otitis media; are they also responsible for other types of respiratory tract infection? This seems likely and it needs further investigation.

Treatment with sulphonamides and antibiotics has been associated with a dramatic decrease of purulent infections of the upper respiratory tract such as otitis media, mastoiditis and peritonsillar abscess, which underlines the importance of bacterial infection at these sites. In these conditions their role is undisputed and the use of such drugs as penicillin, erythromycin and co-trimoxazole is fully justified. Unfortunately, they are used indiscriminately for many other respiratory tract infections. As well as being wasteful, this has given rise to fears that drug-resistant bacterial strains may evolve. Nobody can suppose that the circulation of beta-haemolytic Streptococci, for instance, could be diminished by such treatment, as there are far too many minor infections and carriers, but their use might reduce the transmission of these organisms. However, practitioners have come to rely upon these drugs because they appear to encounter fewer complications when they are used. This is, I think, the important factor, rather than the pressure of patients, their relations or drug manufacturers.

Future needs

Further research is clearly needed to evaluate the new drugs that are becoming available and those that have long been in regular use. It is indeed astonishing that no adequate trials have ever been carried out on the use of antibiotics in many types of acute respiratory infection. The

cost of treating these ubiquitous infections represents a substantial item on the nation's drug bill and action is long overdue.

The majority of respiratory infections do not require hospital treatment and general practice provides better opportunities for their study. Over a sufficient period, representative samples of the full range of these infections can be studied and their clinical symptomatology correlated with the results of laboratory tests. The results of the clinical methods that I have described and the recent advances in virological diagnostic techniques suggest that new investigations in general practice should lead to important new knowledge.

The role of bacterial infections in disease of the upper respiratory tract needs further exploration. In particular, the significance of pneumococcal and *Haemophilus influenzae* infection should be established. The repeated tests on respiratory secretions required for the recovery of organisms and the typing of pneumococci would probably be more easily undertaken in volunteer studies in hospital outpatient departments (Isaacs *et al.* 1983). If some bacteria proved to be of importance, it would provide a more rational basis for the administration of antibiotics in infections in which their value is not yet established.

Finally, pneumococcal and *Haemophilus influenzae* vaccines, which so far have only been tested in restricted groups of patients (Lambert 1980), should be further evaluated by controlled trials in normal children in general practice. This is an extensive programme with many obvious problems but it should lead to more effective treatment and control of these illnesses. We have indeed, for far too long, endured the burden of respiratory infections. Let us hope that we may soon be able to refute the saying of Hippocrates, with which I began this paper.

Acknowledgments: I should like to thank Dr D R Gamble, Director of the Public Health Laboratory, Epsom, and the members of his staff who carried out so much of the work that I have reported here. Dr Gamble has also assisted me with statistical work and with helpful criticism.

References

Celsus (1935) De Medicina, vol I. Translator W G Spencer. Heinemann, London; Book IV, pp 370–371

Chretien J, Holland W, Macklem P, Murray J & Woodcock A (1984) *New England Journal of Medicine* **310,** 982–984

Cockburn W C (1979) *Journal of Infection* **1,** Suppl 2; pp 3–8

Crofton J & Douglas A (1981) Respiratory Diseases. 3rd edn. Blackwell, Oxford; p 150

Dingle J H, Badger G F & Jordan W S (1964) Illness in the Home. Press of the Western Reserve University, Cleveland; pp 5, 19

Fox J P, Elveback L R, Spigland I, Frithingham T E, Stevens D A & Huger M (1966) *American Journal of Epidemiology* **83,** 389–412

Gray B M, Converse G M III & Dillon H C jr (1980) *Journal of Infectious Diseases* **142,** 923–933

Gwaltney J M jr, Hendley J O, Simon G & Jordan W S jr (1967) *Journal of the American Medical Association* **202,** 494–500

Hippocrates (1950) Translator J Chadwick & W N Mann. Blackwell, Oxford; p 23

Holland W W (1982) *Thorax* **37,** 401–403

Hope-Simpson R E & Higgins P G (1969) Progress in Medical Virology. Karger, Basel; vol 11, pp 354–407

Howard J E, Nelson J D, Clahsen J & Jackson L H (1976) *American Journal of Diseases of Children* **130,** 965–970

Isaacs D, Flowers D, Clarke J R, Valman H B & Macnaughton M R (1983) *Archives of Disease in Childhood* **58,** 500–503

Lambert H P (1980) *Archives of Disease in Childhood* **55,** 915–916

Logan W P D & Cushion A A (1958) Morbidity Statistics from General Practice, vol 1. HMSO, London; pp 76–78

Miller D L (1973) *Postgraduate Medical Journal* **49,** 749–762

Poole P M & Tobin J O'H (1973) *Postgraduate Medical Journal* **49,** 778–787

Reid D D (1969) *Proceedings of the Royal Society of Medicine* **62,** 311–316

Royal College of General Practitioners/OPCS/DHSS (1979) Morbidity Statistics from General Practice 1971–72 (Studies on Medical Population Subjects No. 36). HMSO, London

Townsend J G & Sydenstricker E (1927) *Public Health Reports (Washington)* **42,** 99–121

Van Volkenburg V A & Frost W H (1933) *American Journal of Hygiene* **17,** 122–153