A survey of infectious mononucleosis in the North-East Regional Hospital Board area of Scotland, 1960–9

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SUMMARY

This report, based largely on 1258 laboratory proven cases of infectious mono-nucleosis (IM) detected in the North-Eastern Regional Board area of Scotland during the years 1960–9 inclusive, describes and discusses some of the epidemiological and diagnostic aspects of the disease.

During the period of study, the annual rate of incidence increased fourfold from 11·1 to 44·3 cases per 100,000 population. Evidence is presented to indicate that this does not represent a true increase in prevalence but reflects improvements in disease detection. The annual incidence rates as reported by the C.D.S. for 1967–9 inclusive are regarded as a considerable underestimation of the 'true' incidence of the disease. Over a 3-year period an annual incidence equivalent to 100 per 100,000 population was found in each of two selected group practices. This value was constant and is thought to approximate the 'true' incidence of symptomatic, seropositive IM in the general community.

Of the 1258 seropositive cases, 48·7 % were males and 51·3 % females. The peak age incidence was 15–19 years for both sexes. Twenty-one per cent of the cases were in children under 15 years and only 8·1 % in adults older than 25 years. No significant variation was found in the seasonal or urban/rural incidence. Marked differences were found in the leucocyte patterns of seropositive and 'seronegative' cases.

INTRODUCTION

No long-term study of the incidence and distribution of infectious mono-nucleosis (IM) in the general community has been previously reported. This communication, based mainly on 1258 seropositive cases detected in the North-East Regional Hospital Board area of Scotland during the years 1960–9 inclusive, describes and discusses some of the epidemiological and diagnostic aspects of the disease and compares the findings with published data mainly derived from short-term studies of special population groups.

MATERIALS AND METHODS

The North-East Regional Hospital Board area of Scotland comprises the City of Aberdeen, the mainland counties of Aberdeen, Kincardine, Banff and Moray and the island counties of Orkney and Shetland. The total regional population at the 1961 census was 479,421 persons. This region is eminently suitable for the epi-

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demiological study of IM by reason of its geography and the almost unique role of the laboratory based at the City Hospital, Aberdeen. For almost 50 years this has provided a comprehensive postal laboratory service to the general practitioners of the entire region and, amongst other duties, has also met the laboratory needs of the infectious diseases unit situated at the same hospital.

The major part of this survey is based on the results of 8828 heterophile-antibody tests carried out in the laboratory during the years 1960–9 inclusive. Of the 1258 seropositive results recorded only 9·1 % were derived from hospital in-patients. The data relating to the years 1960–3 inclusive were retrospectively obtained from the laboratory records but thereafter all information was derived prospectively.

The serum or whole blood samples (usually both) were submitted from patients with clinical features suggestive of IM, mainly by general practitioners or the infectious diseases unit. In addition to heterophile-antibody tests, detailed examination of the peripheral blood was undertaken in almost all cases. In many instances more than one blood specimen was received for examination, while repeat examination was routinely requested on those patients who were strongly suspected of having the disease on clinical or haematological grounds but whose serum gave a negative heterophile-antibody test at the initial investigation.

For the purpose of this study, the diagnosis of IM was accepted solely on the basis of the conventionally recognized differential absorption (DA) test. Thus suspects showing the clinical or haematological features of IM were considered to have the disease only if the DA test was positive. Such patients have been termed seropositive. The remaining suspects, i.e. those failing to give a positive DA test on one or more occasions, have, for convenience, been termed 'seronegative'. Further diagnostic differentiation of the latter was impossible because of their vast number, wide source of referral, and the lack of first-hand knowledge of their clinical features. Thus they obviously include a variety of different diseases which may have simulated IM only in their clinical presentation.

Details of the serological methods and the diagnostic criteria applied in this laboratory for the diagnosis of IM have been fully described elsewhere (Davidson, 1967). Briefly, all sera were initially screened by a slide technique, a modification of the sheep-cell test (Moloney & Malzone, 1949) being used until 1966, after which time the method of Hoff & Bauer (1965), using a 4 % saline suspension of formalin-treated horse erythrocytes as antigen, was adopted as the routine procedure. All sera reacting positively with the screening test were then subjected to a full DA test. In this laboratory the lowest titres accepted as being diagnostic are 1/64 before and 1/32 after absorption with guinea-pig kidney. Peripheral blood investigations were carried out according to standard methods and included microscopic examination of a freshly prepared Leishman-stained film.

RESULTS

Annual incidence

The annual number and incidence of the 1258 serologically confirmed cases occurring in the years 1960–9 inclusive and the ratio of seropositive to 'seronegative' cases are shown in Table 1. During the period of study it would appear that the incidence of seropositive cases has increased fourfold. Such an interpretation is seen to be quite fallacious, however, when the 'seronegative' cases recorded during the same period are taken into account. Thus, the apparent and progressive increase in incidence is seen to parallel the rise in the number of heterophile antibody tests performed and the ratio of seropositive to 'seronegative' cases has remained relatively constant throughout. The mean ratio of 1/6 also supports the belief that clinical diagnosis alone is unreliable.

Table 1. *Annual incidence of infectious mononucleosis in the North-East Region of Scotland, and ratio of seropositive to 'seronegative' cases (1960–9)*

	Number of cases		Ratio of positive/ 'negative'	Seropositive cases (rate per 100,000 population)
Year	Sero- positive	'Sero- negative'		
1960	53	300	1:5·7	11·1
1961	81	433	1:5·3	16·9
1962	61	484	1:7·9	12·7
1963	101	665	1:6·7	21·1
1964	101	712	1:7·0	21·1
1965	134	838	1:6·3	27·9
1966	154	872	1:5·7	32·1
1967	165	1042	1:6·3	34·4
1968	196	1014	1:5·2	40·9
1969	212	1210	1:5·7	44·3
	1258	7570	1:6	

The author considers the recorded rates to be a substantial underestimate of the 'true' prevalence of the disease in the community because, during the study, it soon became apparent that a fair number of practitioners in the region were sending few, if any, blood samples to the laboratory from IM suspects.

A detailed study was therefore made of the number of suspected cases referred for laboratory investigation by two group practices selected on the grounds that the doctors were both alert to the disease and laboratory-minded. The seven practitioners involved were not informed that the study was being undertaken. One practice (A) was rural with a list of approximately 5000 patients, while the other (B) was urban with approximately 10,000 patients.

During the 3 years 1966–8 inclusive, practice A submitted specimens from 24, 27 and 29 IM suspects respectively and of these 6, 6 and 7 gave a positive DA test. During the same years, practice B referred samples from 49, 52 and 50 suspected cases of which 10, 9 and 10 gave positive serological results.

Thus for both practices, the annual incidence of seropositive cases appears relatively constant and is equivalent to 100 per 100,000 population, while the ratio

of seropositive/'seronegative' cases also shows little variation but is significantly lower than the mean regional value of 1:6.

Based on this information and an intimate knowledge of the region, the author considers that a reasonably accurate estimate of the annual incidence of seropositive, symptomatic IM occurring in the general community approximates 100 per 100,000 population.

Table 2. *Comparison of reported incidence of seropositive cases in the North-East Region and the rest of Scotland* (1967–9)

	No. of cases		Rate per 100,000 population at risk	
Year	N.E. region	Rest of Scotland	N.E. region	Rest of Scotland
1967	158	528	32·9	11·2
1968	169	545	35·3	11·6
1969	208	644	43·4	13·7

In contrast to these findings, Table 2 records and compares the annual number and incidence of seropositive cases of the disease reported weekly to the Communicable Diseases Scotland (CDS) during 1967–9 inclusive, by this and all other hospital laboratories in Scotland.

Firstly, it is pointed out that although the weekly notifications are conscientiously made by this laboratory, 38 cases were not reported to the CDS during the years 1967–9. Even with this error there is still a threefold difference in the rate recorded for the North-East Region compared with that for the rest of Scotland.

It would be erroneous to infer that the disease is three times more prevalent in the North-East but valid to conclude that the disparity is the result of a multiplicity of factors broadly relating to one or other of two main variables: (*a*) regional variations in the number or proportion of suspected cases referred for laboratory investigation, and (*b*) variations in the accuracy with which these laboratories notify the seropositive cases.

Finally, these results would appear to cast grave doubts on the value and validity of extensive national surveys, a view acknowledged by Newell (1967) after attempting to conduct a similar type of survey in England and Wales.

Age and sex incidence

Of the 1258 seropositive cases reported in this survey, 612 (48·7 %) were males and 646 (51·3 %) were females. The age and sex incidence per 100,000 population at risk is recorded in Table 3 and reveals, as in most other studies, a very low incidence in infancy and in adults over 30 years of age, with the peak incidence occurring in the 15–19 age group for both sexes. Although the peak incidence for both sexes occurs in this age group, a significant difference is seen to exist between the sexes in the rates of incidence within the ages of 15–24 years. Thus within the

15–19 age group, 56·3 % of the cases were female, while in the 20–24 age group only 39·2 % were female.

For comparison, the age incidence of 2056 'seronegative' cases (1022 males and 1034 females) occurring in 1967–8 inclusive is shown in Table 4. In contrast to the above findings, the incidence is seen to be uniformly higher for all age groups and presents a less well defined age distribution.

Table 3. *Age and sex incidence of seropositive cases per* 100,000
population per year (1960–9)

	Rate per 100,000 population	
Age group	Males	Females
0–4	2·4	0·5
5–9	26·7	31·0
10–14	26·5	40·1
15–19	148·7	186·4
20–24	132·6	79·0
25–29	20·5	15·7
30 and older	2·1	2·4
All ages	26·8	25·6

Table 4. *Age incidence of 'seronegative' cases per* 100,000
population (1967 and 1968)

Age group	No. of 'seronegative' cases	Rate per 100,000 population per year
0–4	63	78·5
5–9	267	350·0
10–14	305	358·3
15–19	385	562·8
20–24	349	582·2
25–29	160	267·5
30 and over	527	99·6
All ages	2056	214·4

Seasonal distribution

Table 5 shows the seasonal distribution of the total 8828 suspected cases investigated during the years 1960–9 inclusive. As can be clearly seen, there is no significant variation in the seasonal incidence of seropositive or 'seronegative' cases.

Rural/urban distribution

No significant difference was found in the rate of incidence of serologically confirmed cases occurring in the rural and urban (City of Aberdeen) communities of the region.

*Comparison of leucocyte patterns in seropositive
and 'seronegative' cases*

Table 6 compares some of the leucocyte changes observed in the initial peripheral blood examination of 330 seropositive and 768 'seronegative' cases. In the

seropositive group the salient features are that almost 50 % of cases had a definite leucocytosis and 90 % had an absolute lymphocytosis. In contrast, no such clearly defined patterns emerged in the 'seronegative' group of patients. Thus, while 16·6 % had an absolute lymphocytosis, a definite neutrophilia was found in 18 % and an eosinophilia in 9·7 % of the cases. These findings would appear to substantiate the view that several quite different disease entities are included within this group because of failure to differentiate them on clinical grounds.

Table 5. *Seasonal incidence of seropositive and 'negative' cases, 1960–9*

	Jan.–Mar.	Apr.–June	July–Sept.	Oct.–Dec.
Seropositive cases	297	361	276	324
% of total	23·6 %	28·7 %	21·0 %	25·8 %
'Seronegative' cases	1945	2013	1726	1886
% of total	25·7 %	26·6 %	22·8 %	24·9 %

Table 6. *Comparison of leucocyte changes in seropositive and 'seronegative' cases*

	Seropositive (330 cases)	'Seronegative' (768 cases)
Leucocytosis ($> 10{,}000/mm.^3$)	48 %	22·3 %
Leucopenia ($< 3500/mm.^3$)	0·3 %	3·4 %
Lymphocytosis ($> 4500/mm.^3$)	90 %	16·6 %
Neutrophilia ($> 7500/mm.^3$)	0·0 %	18 %
Eosinophilia ($> 500/mm.^3$)	0·9 %	9·7 %

DISCUSSION

General incidence

The overall incidence of IM remains a matter of dispute. Published estimates, reviewed by Penman (1966), have shown enormous disparity, the extremes of variation being 1·6 and 2000 cases per 100,000 population recorded by Newell (1957) and Yeager (1961) respectively.

Such disconcertingly diverse results can be largely attributed to two major differences in classification relating to whether (i) the diagnosis has been established according to clinical or laboratory criteria and (ii) the prevalence rate has been expressed as a composite of both seropositive and 'seronegative' cases. Thus, extremely high prevalence rates have been a feature of those studies relying solely on clinical diagnosis or where seropositive and 'negative' cases have been combined, whereas low rates have generally been found in those studies based on laboratory diagnosis and including only serologically confirmed cases.

Other important factors contributing to the discrepancies but to a lesser degree have been (iii) the type of population studied, especially if selection has been age-related as in surveys involving students, nurses and servicemen; (iv) duration and manner of case finding including the diligence and care with which the latter has been pursued; and (v) differences in methods and interpretation of serological tests.

Although most of these shortcomings have been avoided in the present survey it is apparent that the method of case finding or collection has exerted a profound influence on the present results. Thus the annual rate appears to have increased in

direct proportion to the increase in the total number of serological tests carried out, the latter presumably being related to the more extensive use being made of the laboratory by general practitioners and their increased awareness of the disease.

The main flaw in a regional survey of this kind is undoubtedly its dependence on a large number of individual doctors, some 300 in this instance, for case finding and referral. When this major variable was reduced by carrying out a study confined to seven doctors in two selected practices a much higher rate of incidence was attained and, moreover, this rate remained relatively constant over a 3-year period.

The evidence presented in this communication therefore appears to indicate that an annual rate of 100 per 100,000 population is a fairly accurate estimate of the number of seropositive cases with symptoms occurring in the general community.

This value probably represents a minimum for the 'true' incidence of the disease, however, as it does not take into consideration (a) subclinical cases, (b) patients with symptoms who failed to consult their doctor, and (c) patients with delayed heterophile-antibody formation who were initially 'seronegative' and had no follow-up tests.

Subclinical forms of the disease would appear to be of infrequent occurrence according to serological testing of healthy blood donors (Barrett, 1941; Hobson, Lawson & Wigfield, 1958; Virtanen, 1962) and careful surveillance of close contacts of the disease (Hoagland, 1955; Evans & Robinton, 1950). Patients in category (b) may be more numerous, at least in students (Bender, 1958), although it is probably impossible to assess their number in the general community. Finally, a significant number of cases may be missed owing to delayed heterophile antibody formation, but numerical estimation is again difficult because the onset of clinical symptoms can rarely be dated precisely. In this connexion Hobson *et al.* (1958) found that in 205 cases, where the onset of symptoms could be reasonably defined, a positive heterophile-antibody reaction was obtained in 69 % by the 14th day of the illness, in 90 % by the 21st day and in 94 % by the 28th day. In contrast, Hoagland (1952) recorded seropositive results in 95·3 % of cases within the first 2 weeks of the illness.

Is the incidence of the disease increasing?

Little factual information is available from reliable sources to substantiate the prevailing view that the incidence of the disease is increasing.

Thus an analysis of 1779 cases hospitalized in Stockholm during the years 1940–57 demonstrated a fourfold increase in incidence from 5·3 to 23·2 cases per 100,000 (Ström, 1960). Even allowing for the influence of changes in the social, medical and diagnostic conditions, this was regarded as representing a true increase in disease prevalence.

During the period 1943–8, 79 cases of seropositive IM, equivalent to an annual incidence of 3·25 cases per 100,000, were diagnosed in the North-East area of Scotland (Fullerton & Smith, 1951). In 1969 the annual rate recorded by the same laboratory was 44·3 cases per 100,000, which represents a 13-fold increase over a 25-year period. The question is, does this indicate a real increase in prevalence?

As stated earlier, the gradual increase evidenced over the years may largely be a function of an increasing awareness of the disease on the part of general practitioners, and the submission by them of an increasing number of suspected cases to laboratory investigation.

In addition there is strong supportive evidence that the annual incidence in two selected practices was relatively constant at an equivalent rate of 100 cases per 100,000, which is $2\frac{1}{2}$ times above the current rate for the entire region.

Thus one may reasonably conclude that, during the period of study, no real increase in the prevalence of seropositive glandular fever occurred within the area and the apparent increase merely reflects improvements in disease detection. In some other areas it is probable that higher rates of detection have been achieved since the recent introduction of simplified serological methods which have enabled more laboratories to provide at least a screening service.

Finally, it is suggested that if changes in the incidence of the disease in the general community are to be satisfactorily monitored, their study should be confined to selected group practices.

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