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The incidence of glandular fever

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Published estimates of the incidence of illnesses described as glandular fever or infectious mononucleosis (regarded as synonymous in this paper) have varied enormously. The figures given have presumably been influenced by the methods used for diagnosis, by the type of community studied, and by the thoroughness of case finding. It is thus very difficult to know how frequently this disease presents in the general community. The present paper reports an attempt to determine the incidence of cases of proved glandular fever presenting to general practitioners in certain communities near Portsmouth, Hants.

Previous reports

Glandular fever has been notifiable in Bristol since 1960, and special efforts have been made there to find as many cases as possible. The apparent annual incidence of the disease has been increasing, and in 1963 and 1964 about 30 confirmed cases were found per 100,000 population (Medical Officer of Health, Bristol, 1960–64). Hobson, Lawson & Wigfield (1958) searched for cases in Oxford city with the co-operation of general practitioners, and diagnosed glandular fever on the basis of laboratory findings. They found an annual case incidence of 68 per 100,000 population (seronegative cases included). Oxford, however, is unrepresentative of the country as a whole, particularly in respect of glandular fever, because of the presence of large numbers of subjects (students and nurses) of an age especially liable to the disease. Those studying populations composed mainly of adolescent or young adult subjects find an even higher incidence; thus, Rugg-Gunn (1954), Evans (1960) and Yeager (1961) found annual rates equivalent to 171, 450 and 2000 respectively per 100,000 population.

Some reports deal with cases of glandular fever admitted to hospital. Ström (1960) in Stockholm and Belfrage (1962) in Malmö, Sweden, gave figures which indicate annual admission rates for this disease of about 23 and 30 per 100,000 population respectively (seronegative cases included) in 1955–57. Other reports deal with the incidence in the general community, the figures being derived from the number of positive serological tests for this disease recorded in laboratories. Thus, Newell (1957) reported an annual incidence of between 1·6 and 5·9 per 100,000 population in England and Wales. Virtanen (1962*a*, *b*), also using this approach, gave figures for Turku, Finland, indicating incidences of 4·5 and 6 per 100,000 population in 1960 and 1961 respectively. In neither Newell's nor Virtanen's work were special efforts made to find as many cases of glandular fever as possible, and Newell

acknowledged that his figures underestimated the incidence even of laboratory diagnosis of the disease.

Glandular fever became notifiable in Northern Ireland in 1949. The highest recorded annual incidence in that country up to 1962, however, was only 7·7 per 100,000 (Registrar General for Northern Ireland, 1949–1962). Glandular fever and infectious mononucleosis were among the diseases recorded by general practitioners from 106 practices in 1955–56 for the statistical study by the College of General Practitioners and the General Register Office. The 'patient consultation rate' for the two diseases together was 60 per 100,000 in the year (Logan & Cushion, 1958), but an incidence of 110 per 100,000 was recorded from certain selected practices in the south of England. Laboratory confirmation of the diagnosis was not required of doctors contributing to this study.

An altogether different incidence is suggested by the results of tests on the sera of healthy blood donors for the sheep-cell agglutinins typical of glandular fever. Barrett (1941), Hobson *et al.* (1958), and Virtanen (1962*b*) found such agglutinins in about 1 % of donor sera. Assuming that these agglutinins are rare except during and after glandular fever (Davidsohn, Stern & Kashiwagi, 1951), and that they persist for an average of three months (Kaufman, 1944; Davidsohn *et al.* 1951; Hoagland, 1952; Leibowitz, 1953), this finding implies that each year about 4000 per 100,000 blood donors have glandular fever with the transient appearance of sheep-cell agglutinins.

Not only is there dispute as to the overall incidence of glandular fever. The age incidence is also a point of disagreement. Most authors studying general populations and using laboratory methods of diagnosis find that only a quarter to a third of patients with glandular fever are aged less than 15 years (Press, Shlevin & Rosen, 1945; Stevens, Bayrd & Heck, 1951; Ström, 1960; Belfrage, 1962). Only 18 % of Newell's (1957) patients were in this age group. On the other hand, in the purely clinical study referred to above (Logan & Cushion, 1958) the incidence of the disease in those under 15 years was found to be 2½ times the incidence in those aged from 15 to 45. The discrepancy between the latter two findings is particularly striking since both the studies concerned covered England and Wales and were almost simultaneous. Such a discrepancy would occur if a clinical diagnosis of glandular fever in children is even more often mistaken than in adults.

The present investigation

A detailed investigation is now reported concerning the incidence of glandular fever in certain general communities near Portsmouth in 1962–63.

MATERIAL

The investigation was conducted in Petersfield urban district (together with certain hamlets in the surrounding rural district), in the town of Emsworth, and in the council housing estate of Leigh Park, north of Havant, Hants. The mid-1963 populations for these areas, as calculated from figures given by the local authorities, were 9450, 7800 and 27,550 respectively (figures to the nearest 50). Each of the areas is served by a weekly pathology clinic to which general practitioners refer

patients for blood tests. The work was carried out continuously for 12 months from October 1962.

Before the work started, all the general practitioners of the three districts were asked personally if they would let me know of any suspected cases of glandular fever; all agreed to do so. Most of these doctors were known personally to me, and would in any case have referred such cases. Patients were seen either at their homes, at the laboratory, or at the weekly clinics. Two patients originally referred with other diagnoses were found to have glandular fever and are included in the survey.

After the end of the year, exhaustive inquiries were made of all the general practitioners to try and trace any cases of glandular fever that might not have come to my attention. No such cases were traced, nor had any patient been admitted during the year, from the three areas, to the Portsmouth hospitals and been given a final diagnosis of glandular fever.

METHODS

A full history was taken and a physical examination made in all cases except five, in which time allowed only of brief details being taken (in these five, routine laboratory tests, only, were undertaken, but in none of them was the diagnosis of glandular fever confirmed). Venous blood was taken in all cases. Almost all patients were seen again between 10 days and 4 weeks later, and in most cases further specimens were taken. Some patients were seen yet again on later occasions.

Total leucocyte counts were carried out in both halves of a Neubauer counting chamber, and the process repeated if the counts differed by more than 10% from their mean. Differential counts were made on 200 consecutive nucleated cells in blood films stained with the Knyvett–Gordon stain.

For the sheep-cell agglutinin test, doubling drop dilutions, up to 1/16, in physiological saline, were made of serum which had been inactivated at 55–56° C. for 30 min. Care was taken to minimize the carrying over in the pipette of excess fluid from tube to tube, and to see that any fluid on the side of a tube was well mixed with that at the bottom. To these dilutions, in one drop volumes in 0·5 × 5·0 cm. tubes, were added equal volumes of a 1–2% suspension of packed, thrice washed, sheep cells in physiological saline, these cells being not less than 1 day and not more than 5 days old. The tubes were tapped to mix the contents, placed first in the 37° C. incubator for 1 hr. and then left at room temperature for 1 hr. They were read after gentle tapping, the highest dilution of serum giving macroscopic agglutination of the red cells being taken as the end-point. The reciprocal of this dilution, calculated after addition of the cell suspension, was the titre taken as the result.

If this test gave a titre higher than 4, or if a preliminary slide-screening test was positive, a full differential absorption test was carried out, using approximately 2% guinea-pig kidney and ox-cell suspensions, and titrating with sheep cells as just described. All the sera were subsequently kept frozen, under sterile conditions, for further investigation; the sheep-cell agglutinin keeps well on storage (Bernstein, 1940; Davidsohn & Lee, 1964). At a later date, those sera which had shown

sheep-cell agglutinins persisting after guinea-pig kidney absorption were retested, using 20% guinea-pig kidney and ox-cell suspensions whose strengths had been checked by centrifuging. Three 0·7–0·8 × 17 cm. tubes were set up; into one were placed four drops of physiological saline, into another five drops of the ox-cell suspension, and into the third five drops of the guinea-pig kidney suspension. A drop of the inactivated serum was added to each tube, the contents gently shaken, and the tubes refrigerated overnight. Those containing antigen were then centrifuged, and doubling drop dilutions in saline made of the supernatants; corresponding dilutions were made of the serum–saline mixture. To each of the dilutions a drop of an accurate 2% suspension of sheep cells was added, and incubation and reading carried out as already described. No changes in the original diagnoses were made as a result of these further tests.

The methods for testing for sheep-cell agglutinins have been described in detail since results vary with the method used (Penman, 1966), and the value of many previously published results of this test has been lost because practical details were not given. Extensive serological, bacteriological and virological investigations were also carried out. The results of efforts to establish a diagnosis in patients shown not to have glandular fever will be the subject of another report.

RESULTS

In the three areas during the year, 53 patients were investigated in whom glandular fever had been suspected clinically, on the basis, *inter alia*, of apparent lymphadenopathy in an acute illness. Two other patients were found to have glandular fever, although this diagnosis had not originally been suspected.

In 17 of these 55 patients there was a mononuclear cell count of at least 4000/mm.^{3} (over 15,000/mm.^{3} in patients aged less than seven years) on at least one occasion, with a minimum of about 25% of these cells appearing atypical. These 17 patients were finally accepted as having had glandular fever. The sera from 13 of them showed sheep-cell agglutinins persisting after guinea-pig kidney absorption, with an overall absorption pattern typical of this disease (Davidsohn *et al.* 1951). The sera from two of the remaining four (one in Petersfield, one in Leigh Park) showed agglutinins persisting after guinea-pig kidney absorption in a special test, using an 0·2% sheep-cell suspension, with microscopic reading of the results. The two absolutely seronegative patients (one in Emsworth, one in Leigh Park) both showed mononuclear cell counts of more than 7000/mm.^{3}; the Emsworth patient showed a raised titre of antibody against *Toxoplasma gondii* (dye-test titre of 64), but, as there was no further rise in two later tests, the significance of this in relation to the current illness was doubtful. The 17 patients with glandular fever include a pupil at a Petersfield boarding school whose home was elsewhere, but exclude a patient whose home was in Petersfield but who suffered the disease away at his place of study. A nurse at St Mary's Hospital, Portsmouth, who returned home to Leigh Park after 12 days' illness, is included.

The geographical distribution of all 55 cases is shown in Table 1: 23 of the 38 (19 male, 19 female, all seronegative) patients shown not to have glandular fever

were aged less than 15 years, but only three of the 17 with glandular fever were in this age group. The four 'serogenative' glandular fever patients were aged 5, 33, 40 and 48 years respectively. The overall annual rate for glandular fever of 38 per 100,000 population means that, on average, one case might have been expected to have presented during the year in any one medium-sized general practice.

Table 1. *Occurrence of unconfirmed and confirmed cases of glandular fever in the three areas*

		Cases investigated		Cases confirmed	
	Mid-1963 population	Total	Annual rate per 100,000 population	Total	Annual rate per 100,000 population
Petersfield	9,450	13	138	6 (8*)	63 (56*)
Emsworth	7,800	13	167	5 (10*)	64 (85*)
Leigh Park	27,550	29	105	6	22
All three areas	44,800	55	123	17	38

* In Petersfield and Emsworth the occurrence of cases of glandular fever was recorded for a further 6 months; the figures in parentheses refer to the results at the end of the whole period of 18 months. The Emsworth figure of 10 includes three seronegative cases, one of which occurred in the first year of the investigation and is mentioned in the text.

The figures for the different areas, however, show that glandular fever apparently presented less frequently in the council housing estate than in either of the other two areas, where most houses are privately owned. This inconsistency may have arisen partly as a result of some cases in the housing estate not being referred for investigation. This possibility is discussed later, but it does seem that glandular fever really was less frequent in the housing estate, since the rate of referral of cases of suspected glandular fever from this area was in fact not much lower than the corresponding rate in the other two areas. The excess of patients with glandular fever in Emsworth and Petersfield did not seem to be accounted for by an undue number of mild cases presenting in these areas.

DISCUSSION

The figure of 38 per 100,000 population for the annual incidence of glandular fever in the general community seems rather low, particularly in relation to the figures, already quoted, for incidence calculated from serological tests on blood donor sera. This suggests either that the family doctors were not referring some of their cases for laboratory confirmation, that many patients ill with glandular fever do not consult their doctors, or that the disease frequently occurs in a subclinical form.

During both the present work and that of Hobson *et al.* (1958), some cases presenting to the family doctors may not have been referred for blood tests because, if the illness was atypical or of short duration, the possibility of glandular fever may not have been considered; even if it was, a venepuncture, particularly in children, may have been thought to be unjustified. In the present work the problem of atypical cases was covered as far as possible in that all the patients referred from

the three areas for blood tests for any reason were seen, and not just those suspected of having glandular fever. It is thought that all the patients in Emsworth and Petersfield suspected by their doctors of having glandular fever have been included in the series. In Leigh Park, however, a small fraction of the population (probably less than 5%) was subsequently discovered not to have been included in the survey. This was because a few families, having moved from the city of Portsmouth to new houses on the estate, retained their old city doctors. Furthermore, in Leigh Park some of the doctors were less well known to me than those in the other two areas. Thus the real difference in incidence of glandular fever between Leigh Park and the other areas may be less than the figures in Table 1 suggest.

The number of patients whose glandular fever causes illness, but who do not consult their doctors, seems impossible to assess. Persons who for long periods do not consult their doctors appear to be healthy (Kessel, 1963), but this does not imply that the 'occasional patient' is perfectly well between consultations. Patients with mild glandular fever have been seen who, had they been so minded, might well not have consulted their doctors. Contratto (1944) and Bender (1958) found many such cases amongst students, and it seems probable that they are not infrequent in this country.

The possible existence of symptomless glandular fever has been investigated by means of haematological and serological examination of contacts of known cases of the disease. Evans & Robinton (1950) and Pejme (1964) have investigated this point thoroughly, but unfortunately obtained different results. The former authors found no good clinical, haematological or serological evidence of infection in contacts of five students who had had glandular fever between two and six weeks previously. Pejme (1964), however, found significantly more atypical cells in contacts of cases than in other healthy subjects, but he did not carry out serological tests on the contacts. Hoagland (1955) examined close contacts of patients with glandular fever and obtained negative differential agglutination results, though the blood of one contact showed 63% lymphocytes, of which 1% were atypical. It might be objected that, since glandular fever is not infectious in the usual sense of the term (Hoagland, 1955), contacts of patients might in any case not be expected to show signs of the disease. However, Hobson *et al.* (1958), on other grounds, thought that there was little evidence of subclinical glandular fever.

It seems then that the figure of 38 per 100,000 population for the annual incidence of glandular fever represents a minimum, Nevertheless, it is likely that, at least in the areas studied and during the time of the present investigation, the incidence of cases presenting to doctors did not greatly exceed this level. How much higher the true incidence might be seems impossible to assess.

The figure of 123 per 100,000 for the annual incidence of illnesses thought possibly to be glandular fever on clinical grounds is remarkably close to the rate of 110 per 100,000 for clinically diagnosed glandular fever found in certain practices in the south of England in 1955–56 (Logan & Cushion, 1958). The present figure of 123 is, in a sense, an over-estimate, for in a few cases in the present work diagnoses other than glandular fever subsequently became obvious on clinical grounds (e.g.

a case of measles). Such cases would not have been included in Logan & Cushion's figures. The present results show that a clinical diagnosis of glandular fever in a child is very likely to be incorrect.

SUMMARY

Previous estimates of the incidence of glandular fever vary widely. Reasons for this are suggested. The present investigation was designed to show the incidence of cases of glandular fever presenting to doctors in certain general communities near Portsmouth in 1962–63.

The overall incidence in these areas during the year was found to be 38 per 100,000 population; this amounts to an average of one case annually in a medium-sized general practice. The incidence appeared to be lowest in a council housing estate. Glandular fever was not common in children, although it was frequently diagnosed on clinical grounds.

The ways in which cases of glandular fever might be missed in a survey such as the present one are discussed. It is thought that many patients may become ill but not consult their doctors. Truly subclinical glandular fever, however, is thought to be infrequent.

This report is based on material included in a thesis accepted for the degree of M.D. at the University of Cambridge.

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