Atypical mononucleosis and glandular fever

Report on a joint study of the South-east Scotland faculty of the Royal College of General Practitioners and the department of haematology, The Royal Infirmary, Edinburgh

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Recorder for the South-east Scotland faculty

GLANDULAR fever, or infectious mononucleosis, is an interesting and baffling disease giving rise to difficulty in diagnosis in general practice. The aetiology of the disease is obscure and there is no specific treatment. Nevertheless, the precise diagnosis is of importance because there are many other diseases which present with similar symptoms and signs including the presence of atypical mononuclear cells in the peripheral blood film, and several of these other conditions are common, require precise therapy, and have a better immediate prognosis.

The clinical syndrome of glandular fever was first described by Pfeiffer in 1889, and renamed infectious mononucleosis by Sprunt and Evans in 1920. In 1923 Downey and McKinley reported the presence in the peripheral blood of atypical cells which resembled primitive monocytes. These abnormal cells had oval or horseshoe-shaped nuclei with abundant bluish-grey cytoplasm that frequently contained azurophil granules. Such cells often showed pseudopodia-like irregularities of the cell membrane and fenestration of the cytoplasm. Downey and McKinley divided these cells into three types—Type III in which the presence of nucleoli and vacuolated dark blue cytoplasm produced an immature appearance, and Types I and II which were characteristically more mature.

In 1932 Paul and Bunnell reported the occurrence in the patient's serum of heterophil antibodies to sheep red blood cells, and in 1934 Tidy wrote a detailed paper in which the classical symptoms and signs of the disease, namely fever, sore throat, enlargement of the lymph glands and malaise were described.

Despite the apparent straight-forward nature of these clinical and laboratory features of the classical form of the disease, difficulty in diagnosis in general practice has arisen from the protean clinical manifestations with which patients may present (Read and Helwig 1945, Vander Meer *et al.* 1945). Many of the organ systems of the body may be affected; central nervous system (Bernstein and Wolff 1950), heart and lungs (Weschler *et al.* 1946), the haemopoietic system (Clarke and Davies 1946), liver (Rosalki *et al.* 1960, Kilpatrick 1966) and the renal tract (Tidy and Morley 1921).

Patients presenting with atypical mononuclear cells in the peripheral blood, even when they show all the clinical features of the disease, may have repeatedly negative Paul-Bunnell tests (Shubert *et al.* 1954, Hobson *et al.* 1958). Moreover these atypical cells may occur in other virus diseases such as upper respiratory tract infections (Warren 1941), tonsillitis (Wilson and Cunningham 1929), measles (Benjamin and Ward 1932), rubella and toxoplasmosis (Whitby and Britton 1963), infectious hepatitis (Havens and Marck 1946), brucellosis (Wise 1943), cytomegalic inclusion disease (Klemola and Kaariäinen 1965), and allergic conditions (Randolph and Gibson 1944).

The presence of atypical mononuclear cells has even been reported in the blood, particularly after contact with anticoagulants, in normal individuals without obvious disease (Efrati and Rosenszajn 1960, Wood and Frenkel 1967).

More recently Wood and Frenkel (1967), in reviewing the literature on the atypical lymphocyte or mononuclear cell, have listed 48 different conditions in which these

abnormal cells can appear in the peripheral blood. Five diseases—infectious mononucleosis, infectious hepatitis, the 'post transfusion' syndrome, para-amino salicyclic acid hypersensitivity, and dilantin and mesantoin hypersensitivity—can produce high counts of these atypical cells, and 18 others lead to low counts. Eight rare conditions comprise a third group, and a further 17 where the causes are poorly documented make up the final fourth group.

In view of the similarity in clinical symptoms and signs of such common conditions as upper respiratory tract infection, tonsillitis, pharyngitis, rubella and, more rarely, mumps and hepatitis, the general practitioner's diagnosis of glandular fever would be simplified if he knew the relationship, if any, between the allegedly specific clinical features of the disease, the serological findings, the numbers of atypical mononuclear cells in the peripheral blood and the results of the liver function tests. Therefore, the purpose of this study was to investigate these relationships in detail, the following method being used.

Method

The criterion for the admission of a patient to the survey was the finding of atypical mononuclear cells, as described by Downey and McKinley (1923), in a peripheral blood film made within eight hours of venepuncture from a sequestrene blood sample submitted to the haematology laboratory by one of the participating doctors and such a patient was entered into the survey irrespective of the tentative diagnosis. This implied that, whilst in the majority of such cases, the provisional diagnosis would be glandular fever, there would be others in whom either an alternative or no diagnosis had been made. All such patients entered in the survey were then followed up by their own general practitioners at regular two or three weekly intervals with the submission of clinical reports on a standard questionnaire card, together with further blood samples for full blood count, liver function tests and Paul-Bunnell test.

The follow-up was ended if a significant titre was obtained in respect of the Paul-Bunnell test, if an alternative diagnosis was confirmed beyond all reasonable doubt or, if 12 weeks had elapsed since entry to the trial even if a firm diagnosis had not been made.

In analysis of the results, the Paul-Bunnell test was considered to be positive if sheep red blood cells were agglutinated by the patient's serum in a titre of one in 56 or more before and after absorption with heated guinea-pig kidney emulsion, and provided that no heterophil agglutinins were present after absorption with boiled ox red cell suspension. Such extra tests increase specificity as recommended by Davidsohn *et al.* (1951) and avoid false positive results due to serum sickness antibody and to the antibodies sometimes found in low titre in normal sera.

The liver function tests carried out (normal range in brackets) were serum bilirubin (0.1 to 0.8 mg. per 100 ml.), thymol turbidity (0–4 units), serum alkaline phosphatase (3–13 King-Armstrong (K-A) units for adults; 10–20 K-A units for children aged 0–3 years; and 15–30 K-A units for those aged 10–15 years), serum glutamic oxaloacetic transaminase activity (8–30 units), and serum glutamic pyruvic transaminase activity (8–30 units).

The general practitioner recorded every two or three weeks, at his own discretion, the clinical manifestations under the following headings; the course of the disease as acute, insidious or relapsing, the presence of palpable lymph nodes, of sore throat, pyrexia, palatal petechiae, purpura other than palatal, non-purpuric rashes, enlargement of liver or spleen, jaundice and neurological manifestations. The completed clinical report was then sent to the laboratory along with further blood samples as already described.

Results

Including a three-month pilot study, the survey lasted two-and-a-half years during

which 173 patients (77 males and 96 females) were entered into the trial on the basis of having atypical mononuclear cells in the peripheral blood film; of these, 58 had many such cells present, 40 had moderate numbers and 75 had only a few cells.

The patients were divided into four groups according to whether the differential Paul-Bunnell test, carried out as described above, was seropositive or seronegative. This test was selected because of its specificity in relation to the diagnosis of glandular fever.

Group I contained 67 seropositive patients in all of whom, with one exception, the diagnosis of glandular fever had been made clinically on the initial examination.

Group II contained 38 patients in all of whom the Paul-Bunnell test was negative on two or more occasions, the average period of follow-up being 39 days (range 7–153 days).

Group III comprised 60 patients in whom only one Paul-Bunnell test was obtained and this was negative. Their average follow-up period was ten days; this was insufficient and emphasized one of the research problems in general practice, namely that follow-up is more difficult than with a captive population such as exists in hospital.

There were eight patients in Group IV in whom no record of the Paul-Bunnell test was obtained. This failure was due to several causes such as the young age of the patient, difficult venepuncture or default in attendance. Therefore, this small group will be omitted from further consideration.

Three groups, then, were available for analysis but comparisons are valid only between Group I which contains all the seropositive cases and Group II in which the majority of cases were probably truly seronegative. Group III, because of inadequate follow-up and lack of serial Paul-Bunnell tests, is likely to contain a mixture of seronegative and missed seropositive cases but this group can still be studied usefully on the basis that, if Group III contains a majority of seropositive cases, it can be added to Group I (shown as column '4' in the tables) and compared with Group II (column '2'); likewise, if Group III contains mainly seronegative cases it can be added to Group II (shown as column '5' in the tables) and compared with Group I (column '1'). Such comparisons should be of value in assessing differences between Groups I and II, and may indeed reveal the probable composition of the unknown Group III. If differences between Group I and Group II still stand out, even when this doubtful group is added to Group I, and then to Group II, the existence of these differences is confirmed. If, on the other hand, the differences between Group I and Group II are obliterated by adding the doubtful Group to the seropositive Group I, the propriety of adding Group III to the seronegative Group II is reinforced. Only if differences between Groups I and II are reduced by adding Group III to Group II will relationships between the seropositive group and those of the other groups be insecure.

Age and sex

When the results are examined on the basis of the age and sex prevalence in the sample (table I), there is a striking preponderance of males and females in the 15–19 year age group among the seropositive cases. When this teenage group is compared with the other age groups in Groups I, II and III the differences are significant ($p < .001$), and when the same comparison is made between Group I and the combined Groups II and III, the difference is confirmed. This difference, however, is not significant when Groups I and III are added together and compared with Group II. The higher incidence of glandular fever in the teenage group, therefore, appears to be substantiated and one can also conclude that Group III probably contains a large number of seronegative cases.

There was no significant difference in sex prevalence between Groups I, II and III.

Seasonal incidence

Seasonal incidence was examined by dividing the cases in each of the three groups

into winter (December-February), spring (March-May), summer (June-August), and autumn (September-November). The greatest number of cases appeared to occur during the winter months, with a decrease in the summer and autumn but the reduction

TABLE I
ATYPICAL MONONUCLEOSIS: AGE AND SEX OF PATIENTS

Age in years	(*1*) *Group I Seropositive*		(*2*) *Group II Seronegative Paul-Bunnell test repeatedly negative (P.B. test neg.> 1)*		(*3*) *Group III Seronegative Paul-Bunnell test negative on one occasion only (P.B. test neg. x1)*		(*4*) *Group I plus Group III (Presumed seropositive)*		(*5*) *Group II plus Group III (Presumed seronegative)*	
	M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
0–9	0	1	0	0	8	1	8	2	8	1
10–14	5	3	2	2	3	6	8	9	5	8
15–19	15	18	2	3	7	13	22	31	9	16
20–24	7	14	4	7	2	9	9	23	6	16
25+	1	3	12	6	6	5	7	8	18	11
	28	39	20	18	26	34	54	73	46	52
Total	67		38		60		127		98	

in the summer figures could be due to the absence on holiday during this period of many of the doctors participating in the trial. The differences were not significant except that, when Groups I and III combined were compared with Group II, the winter predominance was marginally so ($\chi^2=7.9$).

Number of atypical mononuclear cells and Paul-Bunnell test

Table II shows the relationship in the cases between the absolute numbers of atypical mononuclear cells in the peripheral blood film and the result of the Paul-Bunnell test. The patients in each Group were divided into subgroups on the basis of having many,

TABLE II
NUMBER OF ATYPICAL MONONUCLEAR CELLS AND PAUL-BUNNELL TEST

Number of atypical cells in blood	(*1*) *Group I Seropositive*	(*2*) *Group II Seronegative Paul-Bunnell test repeatedly negative (P.B. test neg.> 1)*	(*3*) *Group III Seronegative Paul-Bunnell test negative on one occasion only (P.B. test neg. x1)*
Many	40	7	9
Moderate	14	12	12
Few	13	19	39
TOTAL	67	38	60

moderate numbers, or few atypical cells in the peripheral blood, the basis for selection for the subgroup being dependent on the blood film with the highest count in the series of films made in each individual patient. The results show a striking difference, there being a large number of patients in Group I with high counts and few in Group II

and Group III. The overall differences between the Groups are significant ($p < .005$) and when Group I is compared with the combined Groups II and III, this difference becomes highly significant ($p < .0005$). From this one can deduce that a blood film containing a large proportion (e.g. 20 per cent or more of the total white cell count) of atypical cells is much more likely to have a positive Paul-Bunnell test.

Differences between Groups I and III combined and Group II are of borderline significance and this would support the observations made in discussion of table I that Group III should contain a large number of seronegative cases.

The data presented in this table would be enhanced by reporting the actual counts of the atypical cells rather than the arbitrary division in subgroups with many, moderate numbers, or few cells. Many workers have emphasized the diagnostic value of quantitative differences in the numbers of such cells (Heck 1938, Smith 1966). The results with actual counts in 78 patients in this survey, together with a discussion on the diagnostic significance of atypical mononuclear cells in anticoagulated blood, will be reported separately by Dr J. Stuart (1968).

As the number of atypical cells showed no relation to age, sex or season of the year, these factors have not required discussion.

Liver function and Paul-Bunnell test

Liver function test results were available in 68 per cent of the patients but as the volume of blood samples submitted was often insufficient to perform all the five tests after the serological examination had been done, some of the subgroups, as shown in table III, contained small numbers of patients but were still sufficient for statistical analysis.

TABLE III

LIVER FUNCTION AND PAUL-BUNNELL TEST

(The numerator of the figure in brackets represents the number of abnormal cases and the denominator the number tested)

Liver function tests	*Percentage of cases with abnormal levels*		
	(1) Group I Seropositive	*(2) Group II Seronegative (P.B. test neg.> 1)*	*(3) Group III Seronegative (P.B. test neg. x1)*
Alkaline Phosphatase	*25* (9/36)	*3.3* (1/30)	*7.9* (3/38)
Serum Bilirubin	*6.9* (2/29)	*25* (6/24)	*10.3* (3/39)
Thymol Turbidity	*37.5* (6/16)	*11.2* (2/18)	*13.8* (4/29)
SGOT	*47.3* (9/19)	*20* (3/15)	*6.6* (1/15)
SGPT	*54.5* (18/33)	*18.5* (5/27)	*10* (3/30)
Total percentage (with one or more abnormal tests)	*69.1* (27/39)	*35.5* (11/32)	*19.5* (8/41)

For comparison these results have been expressed as percentages and the actual number of abnormal cases out of the total tested in each group is shown alongside in brackets. The table shows that a larger proportion of the seropositive cases had an abnormality of one or other of the liver function tests, of which the enzyme tests were the most frequently disturbed, and that the levels in Group I were raised more often to a greater degree than in all the other tests in the same and other groups. This accords

with the well-recognized fact that a rise in these enzyme levels affords sensitive evidence of acute hepatocellular dysfunction. In the glandular fever group the serum glutamic pyruvate transaminase (SGPT) was abnormal (54.5 per cent) more often than the serum glutamic oxaloacetic transaminase (SGOT) (47.3 per cent).

The differences between the groups, except for the serum bilirubin and thymol turbidity, were statistically significant and highly so in respect of the SGPT ($p < .0005$).

One can conclude that liver dysfunction occurs more frequently in the seropositive group.

Clinical features and Paul-Bunnell test

Comparison of the clinical features in the three groups of patients (table IV) shows no difference in the course of the illness, in the evidence of rashes other than purpura, of jaundice (the numbers affected were small) and of neurological manifestations.

TABLE IV

CLINICAL FEATURES AND PAUL-BUNNELL TEST

(The incidence is expressed as a percentage. The actual number of cases is given in brackets alongside)

Clinical manifestations	*(1) Group I Seropositive (P.B. test positive)*	*(2) Group II Seronegative (P.B. test negative> 1)*	*(3) Group III Seronegative (P.B. test negative x1)*	*(4) Group I plus Group III (Presumed seropositive)*	*(5) Group II plus Group III (Presumed seronegative)*
a. Acute	*17.5* (10)	*8.3* (3)	*10.2* (5)	*14.1* (15)	*9.4* (8)
Course b. Insidious	*70.0* (41)	*69.5* (25)	*79.6* (39)	*74.7* (80)	*75.3* (64)
c. Relapsing ..	*12.5* (7)	*22.2* (8)	*10.2* (5)	*11.2* (12)	*15.3* (13)
No. of cases recorded ..	58	36	49	107	85
Lymphadenopathy	*95.5* (62)	*71.0* (27)	*93.0* (54)	*94.3*(116)	*84.3* (81)
Sore throat	*90.5* (59)	*60.2* (23)	*79.2* (46)	*85.3*(105)	*72.1* (69)
Palatal petechiae	*52.2* (34)	*36.8* (14)	*24.0* (14)	*39.0* (48)	*29.1* (28)
Pyrexia	*86.0* (56)	*73.5* (28)	*60.1* (35)	*74.0* (91)	*65.5* (63)
Purpura	*1.5* (1)	*26.5* (10)	*5.2* (3)	*3.2* (4)	*13.5* (13)
Rash other than purpura ..	*4.6* (3)	*12.5* (4)	*13.8* (8)	*8.9* (11)	*12.5* (12)
Hepatomegaly	*24.6* (16)	*7.5* (2)	*6.9* (4)	*16.2* (20)	*6.5* (6)
Splenomegaly..	*35.4* (23)	*7.9* (3)	*13.8* (8)	*25.2* (31)	*11.5* (11)
Jaundice	*3.1* (2)	*2.6* (1)	*6.9* (4)	*4.8* (6)	*5.4* (5)
Neurological manifestations	*9.3* (6)	*2.6* (1)	*5.2* (3)	*7.3* (9)	*4.3* (4)
No. of cases recorded ..	65	38	58	123	96

Neurological abnormalities, which only occurred in a few patients, were mainly severe headache and neck stiffness, transient nystagmus (one patient) and paraesthesiae (one patient).

The percentages suggest that most patients, whether seropositive or seronegative, have an insidious illness and present with lymphadenopathy, sore throat and pyrexia and, therefore, are indistinguishable on clinical grounds. Nevertheless, when the three groups are analysed statistically in respect of these features, the differences are significant and this is confirmed when Group I is compared with the combined Groups II and III. This suggests, therefore, that these features occur more frequently in the seropositive cases and that Group III resembles Group II more than it does Group I. Indeed when Group I is compared with Groups II and III combined in respect of lymphadenopathy and sore throat, the difference is highly significant ($p < .005$).

Palatal petechiae were noted in all three groups but occurred more frequently in

the seropositive cases and at a significant level ($p < .005$). Likewise, the higher incidence of hepatomegaly and splenomegaly in the seropositive cases compared with the other two groups was significant, the difference for splenomegaly being marked ($p < .0005$).

Although purpuric rashes have been reported in glandular fever (Clarke and Davies 1964), our results (table IV) show a converse relationship. Purpura is significantly more frequent in our seronegative cases even when Group III is added to Group II or Group I for the comparison ($p < .0005$).

Clinical diagnosis and Paul-Bunnell test

A firm diagnosis of glandular fever was made after initial assessment more frequently in the group shown later to be seropositive than in the other two groups ($p < .005$). In Group I, 66 out of the 67 cases were diagnosed initially as glandular fever, the other single diagnosis being mumps. In Group II the initial clinical diagnosis of glandular fever was made in 22 out of the 38 patients. The alternative diagnoses in this group included upper respiratory tract infections, streptococcal tonsillitis, psychoneurosis and benign viral lymphocytosis. In Group III the initial diagnosis of glandular fever was made in 35 out of 60 patients. The alternative labels were rubella (two patients), infectious hepatitis, bleeding stomal ulcer, streptococcal tonsillitis and upper respiratory tract infection (two patients). No diagnosis was reached in the remaining 18 cases.

This wide range of differential diagnoses in patients presenting with a similar type of clinical syndrome, emphasizes the difficulty that the general practitioner has in managing his patient and the need for him to undertake the appropriate laboratory investigations.

Discussion

In general practice many patients present with symptoms and signs of sore throat, pyrexia, enlarged lymph glands and malaise. Fortunately, in the majority, clinical examination with and without the help of bacteriological tests establishes the diagnosis. In patients with tonsillitis, cure after the appropriate course of antibiotics, is quick and complete. However, there are a number of patients in whom recovery is slow and in them the appearance of atypical mononuclear cells in the peripheral blood is not as helpful as was once thought, because it is now known that these cells can occur in an increasing variety of similar illnesses, the majority of which are viral in origin.

The differential Paul-Bunnell test can be an invaluable aid and a strongly positive result is pathognomonic of the disease. In many patients, however, whose symptoms and signs are thought to be typical, the test is negative. A positive test is helpful to the clinician in that he can reassure his patient that recovery will be complete though slower than from the commoner streptococcal throat infection. Again a positive test will restrain the clinician from allowing too speedy a return of his patient to full activity because of the frequency of unsuspected myocarditis and hepatitis in this disease (Dunnet 1963).

In the present series, 58 per cent of the whole sample were seronegative and 49 per cent of those patients in whom their general practitioner had made the clinical diagnosis of glandular fever had a negative Paul-Bunnell test. In the careful study in Oxford by Hobson and his colleagues (1958), one in three of their cases was seronegative and in other larger series reported in the literature the percentage of negative cases has varied from 38 per cent to 69 per cent.

This wide range of results emphasizes the difficulties of defining the criteria for acceptance of a genuine seronegative case as distinct from one in which the peak of a significant titre may have been missed. In one patient in this survey the Paul-Bunnell test became positive nine-and-a-half weeks after the appearance of atypical mononuclear cells in the peripheral blood film. In the series of Hobson *et al.* (1958) the conversion

of a negative titre to a positive occurred in one patient after 89 days. They also reported that a positive Paul-Bunnell test was obtained on first examination in 69 per cent of their cases within 14 days, in 90 per cent within 21 days, and in 94 per cent within 28 days of the onset of the disease. In contradistinction to the time of onset of a positive Paul-Bunnell test, the duration of a significant titre of antibodies in the blood is said by Bernstein (1940) to range from a period as short as two weeks up to as long as six months. One can, therefore, conclude that the patient should have a Paul-Bunnell test done fortnightly for at least 12 weeks so as to avoid missing a transient significant titre. A similar problem occurs with regard to the rise in number of atypical mononuclear cells in the peripheral blood film whose presence usually precedes the positive Paul-Bunnell test. The cells commonly, but not always, disappear before the test becomes negative (Hobson *et al.* 1958).

It was of interest to note that the degree of disability produced by the illness did not always relate to the strength of the Paul-Bunnell titre in a seropositive patient. One patient had an initial titre of 1/224 which rose to 1/1792 after 38 days, yet was quite ill on the first occasion and well on the second. Conversely, another patient had an initial titre of 1/224 which became negative after 16 days and yet he remained seriously ill throughout this period.

Table V summarizes the results shown in previous tables. The seropositive patients are compared with those with more than one seronegative Paul-Bunnell result and it is seen that the seropositive cases appear to occur in a younger teen-age-group. There was no significant difference in sex incidence, a finding that disagrees with Dunnet (1963) who noted that a greater number of females were affected. Most other series reported males to be in the majority (Bernstein 1940, Nyfeldt 1932, Glanzmann 1930) but difficulty in evaluation arises from the fact that the age-sex structure of the population from which patients are drawn is often difficult to ascertain. There was no pattern of seasonal incidence in either of the two groups, cases occurring all the year round but an analysis by individual months suggested a slight predominance of seropositive cases in the winter. Other surveys appear to differ from each other and the only consistent finding is a fall in the number of cases occurring in the summer.

TABLE V
DIAGNOSTIC FEATURES

Characteristic	*Atypical mononucleosis*	
	Group I Seropositive (P.B. test positive)	*Group II Seronegative (P.B. test negative> 1)*
Age	15–24 years	20–25+ years
Sex	No significant difference	
Season	All year but ? peak late winter	All the year
Atypical mononucleosis	Many cells	Few cells
Liver function tests	Two-thirds abnormal	One-third abnormal
Clinical course ..	Indistinguishable clinically in respect of course, lymphadenopathy, sore throat, pyrexia	
Palatal petechiae ..	One-half	Less than one-third
Purpura	Rare	One-quarter
Hepatomegaly ..	Noted in *24.6*	Noted in *7.5*
Splenomegaly ..	Noted in *35.4*	Noted in *7.9*

The mean percentage of atypical mononuclear cells in the seropositive patients was considerably higher than in the seronegative patients. Stuart (1968) who examined in detail the blood films from 78 patients in this series and also 54 films from normal controls reports that the mean percentage of such atypical cells was 26.0 per cent for the seropositive group and 9.6 per cent for the seronegative group. This would suggest that an arbitrary level of ten per cent could be accepted to differentiate between the two groups but some of the films in the seropositive group fell below this level, and some from the seronegative group were above it. Furthermore, atypical cells have been

reported in healthy adults (Vander Meer *et al.* 1945), and in anticoagulated blood films (Wood and Frenkel 1967). Stuart found up to 11 per cent atypical mononuclear cells in his normal controls and he emphasizes that in blood films made from samples anticoagulated by EDTA (sequestrene) a level of above ten per cent of such cells indicated the need for serological investigation. Hobson *et al.* (1958) found few overall differences between their seropositive and seronegative patients but they reported that the atypical mononuclear cells persisted longer in the former group.

Liver function tests were more commonly abnormal in Group I, the enzyme tests (especially the SGPT) being frequently disturbed. This observation accords with that of Dunnett (1963) who thought that the enzyme tests showed the presence of hepatitis in almost every case of glandular fever.

In the present series the clinical course was indistinguishable in the two groups, the main presenting triad of symptoms and signs being lymphadenopathy, sore throat and pyrexia. This agrees with other series reported, including the large one of 300 cases of Read and Helwig (1945) and the 424 cases of Belfrage (1962). An enlarged liver and spleen occurred in 24.6 and 35.4 per cent respectively of the seropositive cases and this was similar to the incidence in many other series (Read and Helwig 1945). Recently Pullen, Wright and Murdoch (1967) reported 56 per cent of their cases had splenomegaly and 35 per cent had hepatomegaly. However, their sample could be criticized as it was a hospital series and, therefore, selected. In this series, six patients only, all seropositive, had to be admitted to hospital—the reasons for admission being either social or severity of illness. Discrepancy between different surveys may be due to varying persistence in seeking to elicit these helpful clinical signs. Tidy (1934) said that 50 per cent of his patients had an enlarged spleen.

Palatal petechiae were not such a useful physical sign in contributing to the distinction between the two groups but, in conjunction with other features, help the clinician towards a diagnosis of glandular fever as the petechiae were more commonly present in the seropositive patients. In Dunnet's series (1963) 41 per cent of his patients with proven glandular fever had palatal petechiae compared with 52.2 per cent in this series.

Table V, therefore, emphasizes the salient differences between the two groups so that, faced with a patient presenting with lymphadenopathy, sore throat, pyrexia, palatal petechiae, an enlarged liver and spleen, disturbed liver function tests, especially in respect of the enzyme assays, and a high count of atypical mononuclear cells in the peripheral blood film, the clinician could make a probable diagnosis of glandular fever even in the presence of a negative Paul-Bunnell test. He might then wish to follow up the patient further with serial blood counts and films and serological tests.

The differences in the seropositive and seronegative cases highlight one of the problems of what one might call the syndrome of glandular fever. Do these differences mean that there are two different diseases caused by different viral agents or rather, as Shubert *et al.* (1954) have suggested, that there is an epidemic variant of the classical glandular fever with its positive Paul-Bunnell test? Recent discoveries by the Henles (1968) in their studies of the EB virus support the theory that this virus might be implicated in the causation of glandular fever although there are still several questions to answer. Might this difference signify merely that the truly seronegative patients either had a smaller dose of the infecting viral agent or their immunological mechanisms have not reacted to the same extent in that particular individual? Or, on the other hand, does the truth lie in the fact that the seronegative group contains a mixture of missed seropositive cases, patients affected by a related virus and other patients suffering from one of the alternative diseases mentioned earlier which produce atypical mononucleosis in the peripheral blood, e.g. toxoplasmosis?

Our results have emphasized the difficulty of establishing an unequivocal diagnosis

of glandular fever on a single clinical and laboratory examination in every case, particularly in so far as the Paul-Bunnell test may become positive early or late in the illness and may return to normal levels within two weeks of the earliest significant titre. The survey does show, however, that in a considerable proportion of patients, where the symptoms and signs are highly suggestive of glandular fever, close supporting evidence will be furnished by the laboratory tests if these are adequately pursued. It also demonstrates the necessity, which was originally anticipated when the survey was formulated, of now following up a series of patients with atypical mononuclear cells in the blood in whom a clinical diagnosis may not be clear over a period of time by serial blood studies on the lines of this survey and by concurrent viral studies. For it is in these patients that the diagnosis is most difficult. A firm diagnosis, in view of the different causes of atypical mononucleosis, is always of aid to the general practitioner so that he can advise accurately on prognosis and management even if there is no specific drug therapy.

Summary

Over a period of 29 months, a study was made of 173 patients presenting with atypical mononucleosis in the peripheral blood, and these patients were divided into groups according to the results of the Paul-Bunnell differential absorption tests.

Comparisons showed that a large number of seronegative patients were clinically indistinguishable from the seropositive group but a large count of atypical mononuclear cells, the presence of hepatomegaly and especially splenomegaly, abnormalities of the serum glutamic oxaloacetic transaminase and especially of the serum glutamic pyruvic transaminase levels, and the presence of palatal petechiae favoured the diagnosis of glandular fever.

The survey demonstrated the desirability of following up with serial blood and viral studies all patients in whom the clinical diagnosis was in doubt.

Acknowledgements

Thanks for help in planning and in the laboratory studies are due to Drs S. H. Davies, and J. Stuart in the department of haematology, and to Professor Whitby and the department of biochemistry in the Royal Infirmary, Edinburgh. Dr B. I. Davies in the department of bacteriology, University of Edinburgh, helped in the serological investigations and statistical advice and computer analysis was obtained from Mr S. Sklaroff of the department of social medicine in the University of Edinburgh. The survey would not have been possible without the co-operation of the following members and associates of the South-east Scotland Faculty of the Royal College of General Practitioners who submitted patients for entry and follow-up in the survey. Drs I. R. W. Alexander, I. M. Allison, J. T. Baldwin, E. S. Blackadder, C. J. Brigelman, A. A. Brown, A. Cruikshank, J. D. Cruikshank, T. E. Dickson, H. P. Dinwoodie, A. G. Donald, W. M. Down, M. Finlay, J. Hill, D. G. Illingworth, J. D. E. Knox, E. V. Kuenssberg, L. Lamont, A. H. D. Large, D. Lee, J. Lipetz, S. Lipetz, A. G. Livingstone, W. E. McDougall, A. McLaren, G. Macnaughton, R. C. Morton, J. S. Munro, M. B. O'Neill, J. S. Patterson, A. A. Robertson, A. J. Simpson, C. Spence, D. G. Strachan, I. H. Stokoe, P. J. Swarbrick, W. P. Thomson and H. Williams.

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Future rôle of the general practitioner in the hospital service. E. O. EVANS, M.B., B.S., D.A. and E. D. MCEWAN, M.B., Ch.B., D.P.H. *Brit. med. J.* 1969. **1,** 172.

Five surveys of the attitudes towards hospital work of different groups of general practitioners were undertaken by a subcommittee of the General Practitioner Liaison Committee of the Birmingham Regional Hospital Board. As a result of these surveys and other studies they conclude that a substantial proportion of general practitioners wish to take part in hospital work and that there is need to create suitable extra hospital posts for general practitioners. There is also need for the linking of hospital posts with practice vacancies in under-doctored areas so as to attract candidates of high calibre.

Interest in hospital work is greatest in general practitioners who have recently qualified, and unless this interest is satisfied early after qualification it tends to wane.