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GLANDULAR FEVER: A FIELD STUDY*

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Ever since Emil Pfeiffer's description in 1889 of the clinical entity glandular fever, this disease, with its negligible mortality and low morbidity, has continued to present a variety of intriguing and unresolved problems.

The purpose behind the present field study was to add to the knowledge of the relationship between the clinical course of the disease and the appearance, duration, and regression of the serological and haematological abnormalities which to-day are considered to provide the laboratory confirmation of a clinical diagnosis. It was hoped that light would be thrown upon the epidemiology, infectivity, incubation period, and possibly upon the process of dissemination.

The field study, lasting for 30 months (July, 1954, to December, 1956), was carried out in the Oxford area normally served by the United Oxford Hospitals, comprising Oxford City, Oxford County, and a portion of North Berkshire. Each general practitioner in this area was invited to notify the Pathological Laboratory of the Radcliffe Infirmary of any suspected case of glandular fever. A pathologist then visited to take blood samples from the patient and any immediate contacts. In all, 1,156 individuals were examined, of whom 498 were suspected on clinical grounds to be cases of glandular fever and 658 were contacts.

Every case in which serological or haematological findings were regarded as significant or suspicious was followed up and the investigations were repeated at intervals of time, which were to some extent dictated by administrative and executive difficulties and the co-operation of the patients. Whenever possible the case was followed until all serological and haematological abnormalities had disappeared. This ideal was realized in only about 25% of cases, largely because clinical recovery and resumption of work often preceded the vanishing-point of the blood changes by many weeks or even months.

Methods

The laboratory investigations in every case included the Paul-Bunnell test and the examination of a blood film, and in most cases a white-cell count.

Paul-Bunnell tests were carried out by a modification of Barrett's (1941) technique. Three separate volumes of each serum are mixed respectively with 4 volumes of saline, 4 volumes of guinea-pig kidney suspension, and 4 volumes of ox-cell suspension, allowed to stand for one hour, and then centrifuged to obtain clear super-

natant samples. A "screening test" is then carried out by adding to 0.25 ml. of the kidney-absorbed serum an equal volume of sheep-cell suspension, centrifuging at low speed, and examining the sedimented cells by eye for agglutination. The absence of agglutination is reported as negative; just perceptible agglutination is reported as "doubtful positive, too weak to titrate," and subsequent investigation has shown that this corresponds to a titre of 1:40 after absorption with guinea-pig kidney. If there is obvious agglutination in the screening test a titration is carried out as follows: doubling dilutions of the saline-diluted and absorbed serum are made; an equal volume of sheep-cell suspension is added to each; the mixtures are incubated for one hour at 37° C., allowed to stand at room temperature for half an hour, and then centrifuged at low speed and examined. The highest titre showing agglutination is recorded. Paul-Bunnell reaction is recorded as positive when a serum has a titre of 1:80 or more after absorption with guinea-pig kidney and shows a reduction in titre of at least two tubes after absorption with ox cells.

White-cell Count.—The white cells were counted using a $\frac{1}{8}$ -in. (4 mm.) objective and Fuchs-Rosenthal counting chamber. In these circumstances it is possible to make a total count of white cells and at the same time differentiate between polymorphonuclear leucocytes and mononuclear cells (lymphocytes, monocytes, and atypical cells). The absolute counts of mononuclear cells referred to in this investigation were derived in this manner and not by the conventional differential counting method.

Assessment of Abnormal Cells.—The cells which are found in films of the blood of patients with glandular fever are characterized by their variable morphology. In most cases cells belonging to one or more of the three types described by Downey and McKinlay (1923) are found. They vary from cells resembling large lymphocytes to large cells with dark-blue cytoplasm, many of which have nucleoli. In this investigation these cells are referred to collectively as "glandular fever cells" (G.F.).

*This field study was undertaken in July, 1954, under the aegis of a committee consisting of Dr. A. M. Cooke and Dr. F. G. Hobson, consulting physicians; Dr. Victoria Smallpeice, consulting paediatrician; Dr. A. H. T. Robb-Smith, director of pathology; Dr. R. G. Macfarlane, clinical pathologist; Dr. J. F. Warin, Dr. T. Anderson, Dr. A. J. Campbell, Dr. N. C. Parfitt, and Dr. H. A. McKenzie-Wintle, medical officers of health for Oxford City, Oxford County, and North Berkshire; Dr. F. Bevan, Dr. A. W. Henderson, and Dr. C. Stringfellow, general practitioners. Secretaries: Dr. Barbara Lawson, 1954-5, and Dr. Mary Wigfield, 1956-7.

cells). No attempt was made to count these cells as a proportion of the total white cells, but each slide was examined carefully, and, from a subjective opinion, the slides on which G.F. cells were found were divided into categories as follows: (1) G.F. cells numerous; (2) G.F. cells present in moderate numbers, both these being reported as haematologically positive (Haem.+); and (3) occasional G.F. cells.

Results

The individuals examined can be conveniently considered in four groups on the basis of the laboratory findings.

Group 1: 242 cases were Paul-Bunnell positive (P.B.+). Group 2: 100 cases were Paul-Bunnell negative (P.B.-) but haematologically positive (Haem.+). In each of these groups G.F. cells were reported "numerous or present in moderate numbers." The symptomatology and clinical findings of the cases in these two groups were found to be very closely comparable, and are considered later.

Group 3: 99 cases were P.B.-, haematologically doubtful—that is, G.F. cells "occasional"; 43 cases were asymptomatic, and 56 showed clinical symptoms or signs possibly compatible with a diagnosis of glandular fever, though it is recognized that many diseases can mimic the clinical manifestations of glandular fever and that "occasional G.F. cells" are reported in many diseases, usually those of viral origin. An alternative diagnosis to the provisional diagnosis of glandular fever was in some cases established later.

Group 4: 715 cases were P.B.-, haematologically normal. This group consisted of asymptomatic contacts and clinically suspect cases with completely negative laboratory findings.

The 814 cases in groups 3 and 4 are excluded, therefore, from further consideration.

Group 1 and Group 2 Cases

The cases in groups 1 and 2 are compared and contrasted. Each of these 342 cases was provisionally regarded as a case of glandular fever; although the follow-up of group 2 cases was less consistent and determined than that of group 1 cases, it was invariably proceeded with in the reasonable expectation that a positive Paul-Bunnell reaction would develop.

Clinical Course

There was no fatal case in the whole series. The clinical features were recorded by two independent clinical observers, the general practitioner in charge of the case and the visiting pathologist, and did not rest upon the clinical observations of one individual. No new clinical facts emerged relating to symptoms and signs which have not been previously reported in the literature of glandular fever.

TABLE I.—Incidence and Priority of Symptoms and Signs

Symptoms and Signs	Group 1 (242 Cases) P.B.+ (%)	Priority	Group 2 (100 Cases) P.B.— Haem.+ (%)	Priority
Enlarged lymph nodes	88	1	80	1
Sore throat	80	2	54	3
Pyrexia	75	3	69	2
Malaise	52	4	46	4
Headache	47.5	5	44	5
Palpable spleen	26	6	14	8
Abdominal symptoms	18	7	25	6
Anorexia	17.5	8	14	8
Ocular	15.5	9	11	9
Rashes	15.5	9	22	7
Stiff neck	11	10	6	11
Myalgia	10	11	9	10
Coryza	7.5	12	11	9
Enlarged liver	5.5	13	2	12
Icterus	5	14	1	13
Nephritis	1	15	0	

Table I shows the percentage incidence and priority of symptoms and signs in the two groups. The close parallelism between the main symptoms and signs was such that on purely clinical grounds it was impossible to distinguish group 1 and group 2 cases in the active disease state.

The clinical course of the disease, however, in the group 2 cases appeared generally to be less severe and recovery more speedy. This clinical observation was supported by the fact that during the 30 months of this field study there were admitted to the Radcliffe Infirmary, Oxford, or to the Slade Fever Hospital, Oxford, 79 patients, of whom, after investigation, 70 were found to be group 1 and 9 group 2.

The grounds for admission were acute illness for diagnosis and investigation (mainly to the Radcliffe Infirmary) or acute illness which for social or domestic reasons could not be treated at home (mainly to the Slade Hospital).

TABLE II

Treated	Group 1	Group 2	Total
Radcliffe Infirmary	18	4	22
Slade Hospital	52	5	57
Hospital total	70	9	79
At home	172	91	263
Total	242	100	342

Table II shows the place of treatment. In 67 of the hospital patients (85%) the illness followed an uneventful course rarely exceeding 10 days' stay; 12 (15%) presented with worrying or unusual clinical features, although each of the 79 ultimately made a complete clinical recovery. The remaining 263 patients (172 group 1, 91 group 2) were treated in their homes by their general practitioners, the disease following an uneventful course with complete clinical recovery.

Summary of 12 Unusual Cases

All 12 patients presenting with worrying or unusual clinical features were group 1 cases (5%); brief details are given below.

Radcliffe Infirmary

Case 1.—Man aged 23. Presenting symptom—haematemesis and abdominal pain.

Case 2.—Man aged 21. A known haemophilic under treatment (including multiple transfusions) for a retroperitoneal haematoma with complications developed an attack of glandular fever while in hospital.

Case 3.—Man aged 30. Acute onset with rigors, headache, vomiting, and delirious on admission. C.S.F. normal.

Case 4.—Girl aged 7. Admitted with dysphagia and respiratory obstruction secondary to a severe anginous attack with cervical adenitis and superimposed infection with *Candida albicans*.

Case 5.—Man aged 23. Severe hepatitis, sequel to an attack of glandular fever.

Case 6.—Boy aged 7. Persistent fever, erythematous rash, epistaxis, and hepatitis.

Case 7.—Girl aged 5. Pyrexia, drowsiness, vomiting, and periorbital oedema with transient albuminuria and impairment of renal function.

Case 8.—Man aged 24. Tonsillitis, cervical adenitis, papular rash with petechiae, thrombocytopenia, and nephritis.

Case 9.—Woman aged 20. Known and controlled diabetic—temporary disturbance of control of diabetes—afebrile.

Slade Hospital

Case 1.—Girl aged 18. Jaundice and menorrhagia.

Case 2.—Man aged 24. Jaundice.

Case 3.—Man aged 39. Very severe and protracted jaundice and hepatitis.

Yearly Trend and Seasonal Incidence

The yearly trend and seasonal incidence in groups 1 and 2 are shown in Table III. In each of the two complete years (1955 and 1956) there was a marked increase in group 1

cases in April, May, June, and July. Group 2 cases showed no such regular seasonal incidence. In 1954 there was a rise in August, the explanation of which was not obvious. In 1955 there was a rise in November, equally inexplicable. In 1956 there was a rise in July, which was directly attributable to an identified "epidemic" in an Army hospital.

TABLE III.—Seasonal Incidence

	Group 1 (242)			Group 2 (100)		
	1954	1955	1956	1954	1955	1956
January ..		5	9		3	2
February ..		4	9		—	3
March ..		7	5		3	2
April ..		11	13		2	6
May ..		13	23		2	3
June ..		9	11		1	3
July ..	4	9	10	3	1	16
August ..	4	6	4	9	2	3
September ..	7	8	10	—	—	1
October ..	10	9	8	2	2	5
November ..	7	8	9	3	12	5
December ..	3	4	3	5	1	—
Total ..	35	93	114	22	29	49

Incidence Related to Sex and Age

The age and sex distribution of groups 1 and 2 are shown in Table IV. In group 1 the age incidence rises sharply to a peak in the decade 20–29, after which it falls even more sharply, whereas in group 2 the peak incidence is in the decade 0–9, with a steady fall thereafter.

TABLE IV.—Age and Sex Incidence

Age	Group 1 P.B. +			Group 2 P.B. — Haem. +		
	M	F	Total	M	F	Total
0–9 ..	13	6	19	26	12	38
10–19 ..	21	56	77	19	5	24
20–29 ..	85	36	121	12	8	20
30–39 ..	5	7	12	6	4	10
40–49 ..	2	3	5	1	—	1
50–59 ..	2	2	4	—	—	—
60+ ..	—	—	—	—	—	—
Not known ..	1	3	4	2	4	6
Total ..	129	113	242	67	33	100

There is an almost equal distribution between the two sexes in group 1 over the whole range, whereas in group 2 the male:female ratio is 2:1.

In group 1 there is a higher incidence in females in the decade 10–19, which is reversed in the decade 20–29, whereas in group 2 the incidence in males is greater over the whole age range.

In view of the facts that Oxford is a university city and a regional hospital centre, it seemed possible that the influx of students of both sexes at each term, and the considerable numbers of resident nurses, might influence significantly the seasonal, age, and sex incidence of these two disease states. This was not found to be the case. Complete exclusion of all individuals in the above two categories left the main features of incidence unchanged.

Relation of Laboratory Results to Clinical Course

An objective of the present field study was to follow the serological and haematological changes associated with the active disease state until normality was restored.

As mentioned above, this was achieved in only approximately 25% of cases in groups 1 and 2, for a variety of causes beyond any observer control. Such were lack of co-operation by patients who had clinically recovered from the disease and returned to work, movement of patients attending school or university, emotional distress caused by venepuncture in children, etc. The follow-up was regarded as satisfactory and as providing homogeneous data in this 25% because: (1) it could be confidently considered that the first blood samples had been taken within 14 days of "the onset of symptoms," an event which can be in doubt

in a proportion of cases; (2) subsequent examinations had followed at intervals of less than six weeks; in practice, the interval was most usually three to four weeks.

A considerable body of data was also provided by the 75% of cases failing to qualify as above, which nevertheless helped to fill in some details of the pathological and clinical pictures.

A. Paul-Bunnell Test

The technique employed for this test has been described above, along with the system of reporting as positive, doubtful positive too weak to titrate, and negative.

Conversion of P.B.— to P.B.+.—Eleven cases with clinical symptoms and signs showed on the first examination a negative reaction which subsequently became positive. In three cases the date of onset of clinical symptoms was uncertain; in eight cases it could be definitely fixed (see Table V). These eight cases illustrate

TABLE V

Case	Days from Onset	P.B.	G.F. Cells	Days from Onset	P.B.	G.F. Cells
1	1	—	+	16	+	—
2	4	—	+	12	+	—
3	4	—	+	22	+	—
4	7	—	+	16	+	+
5	7	—	+	21	+	+
6	13	—	+	21	+	+
7	18	—	+	41	+	Occasional
8	47	—	+	89	+	—

G.F. cells + = Numerous or moderate. G.F. cells — = None.

several other points: (a) Cases 1–5 had G.F. cells in significant numbers within one week of the onset of symptoms. (b) Cases 1 and 3 show that in rare instances *all* G.F. cells have disappeared from the peripheral blood film by the third week from onset of symptoms, the Paul-Bunnell reaction now being positive. (c) In Case 7 the "occasional G.F. cells" present six weeks from the onset of symptoms may be significant in conjunction with a P.B.+ test indicating a group 1 case. (d) Case 8 illustrates a long delay before the Paul-Bunnell reaction became positive (89 days), all G.F. cells having by now disappeared from the peripheral blood film, although present in significant numbers at 47 days.

Conversion of Doubtful Positive P.B.(+) to P.B.+.—Six cases showing P.B.(+) later became P.B.+ , each being haematologically positive (G.F. cells numerous or moderate) both on the first and subsequent examination, and each with clinical symptoms and signs. Details are shown in Table VI.

TABLE VI

Case	Days from Onset	P.B.	G.F. Cells	Days from Onset	P.B.	G.F. Cells
1	3	(+)	+	8	+	+
2	7	(+)	+	15	+	+
3	11	(+)	+	20	+	+
4	11	(+)	+	20	+	+
5	14	(+)	+	40	+	+
6	26	(+)	+	39	+	+

P.B.(+) = Paul-Bunnell doubtful positive, too weak to titrate.
G.F. cells + = Numerous or moderate numbers.

Reversion of P.B.+ to P.B.(+).—Of 222 cases fully confirmed on the basis of serological (P.B.+), haematological, and clinical evidence, 51 were found to yield a P.B.(+) on average three months after the onset of the disease, when they were asymptomatic. Thus in 57 cases the evidence was absolute that a serum showing a just perceptible agglutination reported as "doubtful positive, too weak to titrate" was significant and indicated that in a group 1 case the disease was either in the course of development or, much more often, that the disease had passed its peak and the serological finding was returning to normal, although many weeks or months after the active clinical manifestations of disease had disappeared. Twenty cases

were found to yield P.B. (+) which could not be followed either to a positive conversion or to a return to normal. Of these, 14 showed symptoms or signs compatible with glandular fever (9 showed G.F. cells numerous or moderate, 5 showed normal films). The remaining 6 had no symptoms and a normal blood film, but all had been intimate contacts of group 1 cases. These 20 cases have been included in the total of 242 P.B.+ cases.

First Appearance of P.B.+—The onset of clinical symptoms can rarely be precisely dated, and laboratory investigations were undertaken as and when requested, but in 205 cases where the date of onset of clinical symptoms could be judged with reasonable certainty a P.B.+ was obtained on the first examination—in 69% of cases by the 14th day, in 90% by the 21st day, and in 94% by the 28th day.

TABLE VII.—Duration of Paul-Bunnell Reaction

Time in Weeks from Onset	Group 1 (P.B.+ Haem.+)				Group 2 (P.B.— Haem.+)	
	59 Cases		66 Cases		34 Cases	
	P.B.+	% P.B.+	Haem.+	% Haem.+	Haem.+	% Haem.+
<2	59	100	66	100	34	100
2	57	97	65	99	24	71
3	56	95	59	89	22	65
4			55	83	15	44
5	53	90	44	67	8	24
6	51	88	33	50	3	9
7	47	80	23	35	2	6
8	45	76	17	26	0	0
9	38	64	11	17		
10	35	59	7	11		
11	28	47	4	6		
12	25	42	3	5		
13	22	37	2	3		
14	20	34	2	3		
15	16	27	1	2		
16	15	25	1	2		
17	13	22	1	2		
18	11	19	1	2		
19			0	0		
20	10	17				
21	8	14				
22						
23	6	10				
24	5	8				
25	3	5				
27	2	3				
33	1	2				
38	0	0				

TABLE VIII.—Shortest and Longest Duration of Positive Paul-Bunnell Reaction from Onset

	Two Shortest Cases			Three Longest Cases	
	Time from Onset	Report		Time from Onset	Report
Case 1 {	5 days	P.B.+	Case A {	11 days	P.B.+
	14 "	P.B.—		38 weeks	P.B.(+)
" 2 {	2 "	P.B.+	" B {	16 days	P.B.+
	16 "	P.B.(+)		63 weeks	P.B.+
			" C {	18 days	P.B.+
				34 weeks	P.B.+

Reversion of P.B.+ to P.B.——In 59 cases the Paul-Bunnell reaction was positive within two weeks of the onset of symptoms and was followed up systematically to the point of reversion to negative (Table VII). The interval between tests in no case exceeded six weeks, and averaged between three and four weeks. Case A (Table VIII) was followed at monthly intervals; in Cases B and C the follow-up was not regular, so that the possibility of relapse and/or reinfection could not be excluded. (Note: One case followed by serial tests, from the onset of clinical symptoms, showed a strongly positive Paul-Bunnell reaction (Haem.+), with steady fall of titre to negative six months later. Then, eight months after the original illness, symptoms and signs recurred and the Paul-Bunnell reaction again became positive. ? Relapse. ? Reinfection.)

B. White-cell Count and G.F. Cells

White-cell Count.—Table IX contrasts the white-cell counts obtained in group 1 cases with those of group 2 as regards both an *absolute* increase of mononuclears—that is, 3,000 per c.mm. or more—and a *relative* increase of mononuclears—that is, 50% or more. It will be seen that group 1, as compared with group 2, has a higher percentage of cases with both an *absolute* and a *relative* increase of mononuclears.

TABLE IX.—Mononuclear Counts

Absolute increase (i.e., mononuclears 3,000 or more in first and/or subsequent counts)

	No. with Monos 3,000 or More	No. with Monos Under 3,000	No. in which Counts were Done	No. with No Detailed Differential Count	Approx. % of Cases Examined with Monos 3,000 or More
Group 1 ..	189	13	202	40	94
" 2 ..	68	18	86	14	79

Relative Increase (i.e., mononuclears 50% or more in first and/or subsequent counts)

	No. with Monos 50% or More	No. with Monos Less than 50%	No. in which Counts were Done	No. with No Detailed Differential Count	Approx. % of Cases Examined with Monos 50% or More
Group 1 ..	179	15	194	48	92
" 2 ..	62	24	86	14	72

G.F. Cells

Direct comparison of the blood films of group 1 and group 2 cases requires some qualification, because in sero-positive cases the evidence of a positive Paul-Bunnell reaction clearly indicates that the case could well be a group 1 case in a regressive phase as regards G.F. cells, which in an average case disappear many weeks before the Paul-Bunnell test reverts to normal.

"G.F. cells present, numerous or in moderate numbers" has been taken as the essentially *positive* report, abbreviated in tables and graphs as "Haem.+ "

"G.F. cells occasional or very infrequent" has been taken as an essentially *negative* report. Such a report, however, was returned on a few cases in definite association with a P.B.+ and/or a fully *positive* blood film on previous or subsequent examinations. In these few cases this finding clearly indicated an incipient or regressive phase of disease group 1 or group 2.

In the absence of previous or subsequent confirmatory serological or haematological evidence, the finding was regarded as excluding group 1 and group 2 disease and indicating a different aetiology.

In group 1 the haematological reports in association with a P.B.+ were as follows: 220 cases, G.F. cells numerous or moderate; 6 cases, G.F. cells occasional; and 16 cases, normal film. In the 22 cases showing G.F. cells occasional or a normal film there was a delay of three to eight weeks in taking the first blood film and often doubt about the date of onset of symptoms. Table VII shows that all G.F. cells disappear from the peripheral blood film in 74% of patients by the eighth week after the onset of symptoms, and may disappear even earlier.

In group 2 there could be no confusion or doubt about the interpretation of the haematological findings, because the diagnosis, by definition, rested simply on the report "G.F. cells present, numerous or in moderate numbers."

Appearance of G.F. Cells

No case was found to be P.B.+ *before* the appearance of G.F. cells, although in regressive phases of the group 1 cases a P.B.+ reaction persisted long *after* all G.F. cells had disappeared.

In most patients the "onset of symptoms" has been rapid, with a prodrome of two to seven days; in a minority the onset has been sudden and could be more precisely dated,

and in a very small number of patients there is evidence to suggest that the onset of the disease state can be so insidious and its clinical course so mild that it passes unnoticed. These observations applied equally to group 1 and group 2 disease, and make it impossible accurately to relate the serological and haematological changes with a precise date.

First Appearance of G.F. Cells.—As was the case with the Paul-Bunnell test, the onset of clinical symptoms can rarely be precisely dated, and laboratory investigations were undertaken as and when requested. G.F. cells were present "numerous or in moderate numbers" on the first examination where the onset of symptoms could be judged with reasonable certainty (Table X).

TABLE X

	No. of Cases	14th Day from Onset	21st Day from Onset	28th Day from Onset
Group 1	206	76%	92%	96%
" 2	80	84%	91%	99%

In group 1, 36 cases, and in group 2, 20 cases, have been excluded because they were first examined *more than four weeks* from the onset of symptoms or because the date of onset was uncertain.

Disappearance of G.F. Cells

In 66 Haem.+ cases of group 1 and 34 Haem.+ cases of group 2, the first positive finding was recorded within 14 days from the onset of symptoms and the changes were systematically followed to the

FIG. 1.—Showing disappearance of G.F. cells (see also Table VII).

vanishing point (see Table VII and Fig. 1). The interval between tests in no case exceeded six weeks and averaged between three and four weeks.

As defined above, this material is homogeneous, but must not be accepted as representing more than an average picture of the peripheral blood film changes. G.F. cells, however, have been found to disappear

earlier and to persist longer than is indicated in Table VII and Fig. 1.

The shortest and longest durations from onset of G.F. cells in blood films are shown in Table XI.

Such findings were rare, but a few cases in each group yielded results showing unusually short or long duration of G.F. cells in the blood film.

TABLE XI

	Time from Onset	Report
Group 1 disease (P.B.+ at all test times)		
Shortest case ..	3 days	G.F. cells in moderate numbers
	12 "	Normal film
Longest ..	14 weeks	G.F. cells in moderate numbers
	18 "	Normal film
Group 2 disease (P.B.-)		
Shortest ..	2 days	G.F. cells in small numbers
	6 "	" " in moderate numbers
	9 "	Normal film
Longest ..	6 weeks	G.F. cells in moderate numbers
	8 "	Normal film

There were a few cases in which G.F. cells were present in the peripheral blood film for greater periods than shown above (group 1, 18 weeks; group 2, 8 weeks), but in these cases the follow-up had been broken and inconsistent, so that there was a possibility of "relapse," "reinfection," or intercurrent illness having disturbed the final blood picture. If these were included in Table VII, the time limit between the onset of symptoms and the disappearance of G.F. cells would be increased.

Conclusions

From the foregoing data and Table VII and Fig. 1, certain conclusions can reasonably be drawn.

Group 1.—A majority of patients are P.B.+ by the 14th day from the onset—a few are P.B.(+) or P.B.— in this early phase; in each of the observed cases when negative or doubtful reactions were obtained the blood film was diagnostic, the Paul-Bunnell conversion following later.

If the Paul-Bunnell test is followed up, a number of cases will be found to yield a P.B.(+) before the reversion to negative. The P.B.+ findings persist approximately twice as long as the G.F. cells in the peripheral blood film. Clinical recovery will have occurred many weeks, even months, before the Paul-Bunnell reaction reverts to negative.

Group 2.—The peripheral blood film does not distinguish group 1 from group 2 cases. By the 14th day from onset 84% of group 2 cases yielded positive films compared with 76% of group 1 cases, but the G.F. cells in group 2 cases disappeared from the peripheral blood in approximately half the time taken in group 1 cases.

In a few cases of either group 1 or group 2 the G.F. cells may appear or disappear earlier or later than the average times indicated by Table VII and Fig. 1.

In assessing the laboratory findings in any given clinical case, it is obvious that the probable phase of the disease must be taken into account, and that, if the findings are equivocal, the investigations should be repeated.

Epidemiology

A major objective of the present study was to collect evidence of the infectivity, mode of dissemination, and incubation period of glandular fever. The very considerable effort to achieve this objective produced the following results.

Military Hospital, Wheatley

Only one small outbreak of disease was identified that could be considered an "epidemic."

Chronology.—May, 1956: Two cases of glandular fever group 1 were admitted to the hospital and discharged for sick leave in the last week of May. June, 1956: In the last week the "epidemic" began, involving members of the hospital staff and long-term in-patients in the wards throughout July and the first week of August.

Fig. 2 shows the course of events, and cases can be identified by the numbers. With the Paul-Bunnell test as a yardstick, the cases fall into two groups.

(a) **Group 1 Disease (P.B.+).**—Three cases, all members of the hospital staff, developed the disease as follows: June 30, No. 2, a nurse; July 20, No. 8, a nurse; August 8, No. 15, a staff sergeant. Cases 2 and 8 were in daily close contact, but neither had any obvious or known contact with Case 15.

(b) **Group 2 Disease (P.B.-).**—There were 12 cases (10 in members of the hospital staff and 2 in long-stay in-patients). These cases can be subdivided: nurses (Nos. 1 and 3), R.A.M.C. orderlies (Nos. 4, 5, 6, 7, 11, 12, and 13), in-patients (Nos. 9 and 10), and medical officer in charge of patients and wards (No. 14).

As shown in Fig. 2, three further group 2 cases were admitted from outside units (one on July 18, July 19, and August 3) which must be regarded as possible additional

FIG. 2.—The Wheatley "epidemic."

TABLE XII

Case No.	Primary Group 1 Case	Age	Contacts		Weeks after Contact with Primary Case	Notes
			No. Examined	No. Positive Group 1		
1	G.W.	10	3 (family)	1 (M.W.)	1	Brothers: ? shared infection
2	R.T.	9	3	1 (B.T.)	3	Same household
3	M.H.	16	4	1 (F.H.)	35	"
4	J.G.	23	1 (college)	1 (R.H.)	3½	"
5	D.T.	22	1	1 (N.D.L.)	4	Adjoining room
6	N.D.L.	20	1	1 (D.P.)	14	Shared "duty"
7	S.H.	18	1 (nurse)	1 (E.M.C.)	2	"
8	J.S.	18	2 (nurses)	1 (E.B.)	12½	Simultaneous, shared duty
9	J.M.	25	1 (office)	1 (A.E.H.)	12	Same office room
10	I.S.	24	1	1 (W.G.G.)	16	See note
11	P.H.	24	1 (fiancé)	1 (R.S.)	Uncertain	"
12	Mrs. S.	30	4 (family)	1 (J.P.)	11½	"
13	Mr. and Mrs. T.	40	1	1 (P.S.)	Uncertain	"
14	G.P.	23	5	1 (D.S.)	14	"
15	G.L.	25	1 (fiancée)	1 (D.T.)	Uncertain	"
				1 (P.P.)	"	"
				1 (E.E.)	"	"

Notes on Cases

Cases 7 and 8.—nurses in the same hospital.
 Case 10 (I.S.).—found to be P.B.+, with normal blood film, no history of illness; suspected as source of infection in R.S.
 Case 12 (Mrs. S.).—found to be P.B.(+) with normal blood film; no history of illness; suspected as source of infection in P.S. and D.S. (her children).
 Case 13 (Mr. and Mrs. T.).—parents of D.T., found to be P.B.(+) with normal blood film; no history of illness; suspected as source of infection in D.T.
 Cases 14 and 15.—the contacts P.P. and E.E. were in each case examined 7 weeks after contact with the primary case. Each case was P.B.(+) and the blood films were normal; there was therefore in each case the possibility of a shared common source of infection, the "primary" case experiencing a full-blown clinical attack, the secondary "contact" having a subclinical attack.

TABLE XIII

Case No.	Primary Group 1 Case	Age	No. Examined	Contacts		Weeks after Contact with Primary Case	Notes
				Group 1	Group 2*		
1	M.F.	8	1 (family)	—	1 (B.F.)	15	Same house
2	H.G.	19	1 (nurse)	1 (J.)	1 (J.P.)	3½	
3	M.	19	1 (nurse)	1 (H.G.)	1 (M.S.)	12½	Nursed M. Shared duty
4	B.J.S.	20	1 (P.O.)	1 (S.)	1 (S.)	Uncertain	
5	M.H.	24	1 (R.A.F.)	1 (J.R.)	1 (J.R.)	½	Friends
6	T.T.	21	1 (college)	1 (M.L.)	1 (M.L.)	6	
7	W.G.G.	18	1 (fiancée)	1 (W.M.)	1 (W.M.)	Uncertain	"

* Each of these group 2 cases was followed up for eight to nine weeks; the Paul-Bunnell reaction remained persistently negative.

Notes on Cases

Cases 2 and 3.—all nurses in same hospital.
 Case 2.—apparent source of infection for group 1 Case J. and group 2 Case J.P., daily contacts.
 Case 4 (B.J.S.).—P.B.+ but normal film; no history of illness; suspected of subclinical attack and source of infection for S.
 Case 7 (W.G.G.).—an office contact of Case 9 (J.M.), in Table XII; circumstances as regards fiancée W.M. difficult to interpret, as her clinical disease (group 2) started six days prior to W.G.G.'s illness.

sources of infection. In summary, the "epidemic" shows a very confused picture with no very obvious attack pattern, and yet it is difficult to exclude an association between group 1 and group 2 cases. Alternatively, it could be maintained that two separate diseases were associated coincidentally in one hospital unit—group 1 cases with an incubation period of about 20 days, group 2 cases with an incubation period of five to eight days.

Other Examples of Associated Infection

Additional to the Wheatley Hospital "epidemic," there were a number of cases of disease in individuals associated by family, social, and occupational contact, or by sharing living accommodation.

Table XII gives details of 15 primary cases of group 1 disease suspected as the source of infection for 17 secondary cases of group 1 disease.

The incubation period in Cases 2, 3, 4, 5, 6, 7, 8 (two cases), 9, 11, and 12 (one case) appears to vary from 2 to 35 weeks. Cases 1, 10, 12 (one case), 13, 14, and 15 are excluded because the evidence is incomplete.

Table XIII gives the details of seven primary group 1 cases suspected as the source of infection for seven secondary cases of group 2 disease and two secondary cases of group 1.

The incubation periods vary from 3 days to 15 weeks.

Relation Between Group 1 and Group 2

The data provided by the Wheatley "epidemic" and Tables XII and XIII pose more questions than answers in relation to infectivity and incubation period. Is there a relationship between group 1 and group 2 cases? Is it conceivable that the association of group 1 primary cases and group 1 and group 2 secondary cases can be purely coincidental?

Arbitrary separation of the cases in the Wheatley epidemic into two separate disease states permits a tentative conclusion as regards the incubation period. That the infectivity is low is the only general conclusion possible.

Table XIV shows the association in five families of five primary group 2 cases with eight secondary group 2 cases.

TABLE XIV

Case No.	Primary Group 2 Cases	Age	Contacts		Days after Contact with Primary Case	Notes
			No. Examined	P.B.—Haem.+ Group 2		
1	R.M.	6	4 (family)	{Z.M. D.M. M.M.}	6	Sister of R.M.
2	R.S.	33	3	{M.S. P.S. D.R.}	10	"Mother", "
3	H.R.	6	None		9	Daughter of R.S.
4	G.S.	6	2 (family)	Mrs. S.	2	Son of R.S.
5	E.J.	7	3	D.J.*	Uncertain	Simultaneous infection. Siblings. Mother of G.S. Brothers

*D.J. showed complete absence of symptoms.

The incubation period in Cases 1, 2, and 4 appeared to be between 4 and 18 days, with the probability of shared infection in Cases 1, 3, and 5. In one family four members, in another three members, were infected, and 10 of the 13 cases were in children under 8 years of age. These facts suggest that in favourable circumstances the disease has a moderately high degree of infectivity, especially in young children.

In these five family groups there was no secondary case of group 1 disease, and the infection appeared to run true.

Incidence of Glandular Fever Among the General Population

Data upon which to base an opinion concerning the incidence of the disease on the general population are meagre

and unsatisfactory because most published epidemiological studies record observations upon selected groups—Service personnel, students, nurses, or hospital admissions.

Further difficulties are that: (1) the disease is not notifiable; (2) there are important differences in the diagnostic standards employed by different laboratories; (3) no attempt is made to confirm a clinical diagnosis in a high proportion of cases; (4) a small number of patients never consult a doctor or have the disease "on their feet."

Newell (1957) analysed the reported incidence of glandular fever on the general population as revealed by the returns of cases identified by a positive Paul-Bunnell reaction from the regional laboratories. He fully recognized that such evidence indicated only the minimal incidence.

In 1955, in the Midland Region as defined by the Registrar-General, there was an incidence of 2.6 per 100,000 of population. For comparison, the population within the boundaries of Oxford City was selected because the profession had been alerted to make full use of laboratory facilities to confirm clinically suspected cases of glandular fever, and this professional co-operation in the field study was likely to be more complete than in the rural areas.

In 1955, in Oxford City, the incidence of P.B.+ cases (group 1) was 56 per 100,000, over 20 times the incidence in the Midland Region in which the city is located. The incidence of P.B.— Haem.+ cases (group 2) was 12 per 100,000, over four times the incidence of the regional incidence of P.B.+ cases. This evidence clearly indicates that there is a higher incidence of P.B.+ (group 1) disease on the general population than has hitherto been recognized.

One further point was examined. While it is certain that a few patients have the disease "on their feet," it is equally probable that this number is very small. In May, June, and July, 1957, the period of highest seasonal incidence, 231 healthy blood donors were examined as controls. Only two positive Paul-Bunnell reactions were found—one in a fully proved case of P.B.+ (group 1) disease two years previously, the other in a patient considered by the doctor to have had glandular fever four months previously but no steps being taken to confirm the clinical diagnosis.

Discussion

The term "glandular fever" has been employed throughout to indicate that in the absence of any known cause the disease state so described must be considered primarily as a clinical entity.

The term "infectious mononucleosis," although favoured and fashionable in recent medical literature, has been avoided as possibly misleading.

The Paul-Bunnell test with full absorption technique was applied to 498 patients suspected to have glandular fever on clinical grounds; 242 were cases of group 1 disease (P.B.+), 100 were cases of group 2 disease (P.B.— but Haem.+), and 156 were due to other causes.

The Paul-Bunnell test in conjunction with the white-cell count and the presence of G.F. cells in significant numbers separated the clinical material into two possibly distinct disease states, the similar and dissimilar characteristics of which can be set out conveniently in tabular form (Table XV).

G.F. cells present in comparable and significant numbers about the 14th day in each disease state are found to persist twice as long in the P.B.+ cases as in the P.B.— cases.

From the purely clinical point of view, group 1 cases have been distinguished from group 2 cases as being on the whole more severely ill and presenting some worrying clinical pictures.

The seasonal, age, and sex incidence of the two disease states present unequivocal differences which have been illustrated in the earlier part of the paper.

The infectivity of either disease is low by comparison with other infectious diseases of viral or bacterial origin.

TABLE XV

Characteristic	Glandular Fever	
	242 Cases (Group 1) P.B.+	100 Cases (Group 2) P.B.— Haem.+
Clinical symptoms and signs	Indistinguishable as regards onset, symptoms, and clinical signs	
Mortality	Nil	Nil
Morbidity: severity	Severe or moderately severe; 5% gave cause for anxiety	Moderately severe to mild; in retrospect a milder disease
Undetected cases	Rare; occasional	Rare; occasional
Seasonal incidence	Increase in April, May, June, July	No regular seasonal changes detected, occasional peaks
Age incidence	Rapid rise to 20–29 age group, followed by rapid fall	Maximal 0–9 age group, with steady fall thereafter
Sex	Overall equal M. and F., but age-group differences	Males exceed females throughout age groups and overall 2:1
Epidemiology, infectivity	Probable but unproved low infectivity	Low infectivity, but definitely infectious. Five family "epidemics"
Incubation	3 days to 35 weeks	4 to 10 days
Association: Groups 1 and 2	Occasional group 2 cases with primary group 1 cases	No group 1 cases with primary group 2 cases
Haematology	W.B.C. and G.F. cell count indistinguishable in active disease state; approx. 80% fully positive by 14th day, i.e., G.F. cells numerous or moderate numbers 6th week, 50% still show G.F. cells 19th week, normal film	5th week, 25% still show G.F. cells 8th week, normal film

The problem of nomenclature, in the absence of a known aetiology, is very real and cannot be lightly dismissed.

If the term "infectious mononucleosis" is considered preferable to the term "glandular fever," what are to be regarded as the definitive diagnostic criteria?

In the absence of any more reliable evidence, the clinician is dependent upon the evidence provided by the Paul-Bunnell test and examination of the peripheral blood film; the technique of the former and the precision of differentiation of the latter have been established for nearly 20 years (Downey and McKinlay, 1923; Davidsohn, 1938; Barrett, 1941). The use of improved techniques upon the available clinical material has multiplied the clinical problems.

If a positive Paul-Bunnell reaction is considered essential to establish a diagnosis of glandular fever (infectious mononucleosis), it has been shown that in the present field study one in every three of clinically suspect cases is seronegative and fails to qualify.

In the past 17 years similar results have been obtained by many clinical observers, who, faced with this problem of definition and nomenclature, have found a solution in a variety of ways, three of which are considered.

Leibowitz (1956), in a fighting retreat from the position adopted by him in 1953 that a positive Paul-Bunnell test "can be utilized as an almost absolute yardstick for the diagnosis of infectious mononucleosis," now considers that "the validity of the diagnosis of infectious mononucleosis in seronegative cases still remains to be established with certainty, and will continue in some doubt until the aetiological agent is identified and an unquestioned diagnostic test results."

Niederman (1956), reviewing cases admitted to the Yale-New Haven Medical Centre, 1946–55, found 166 "clinically acceptable" as cases of infectious mononucleosis, and considered these 72 seropositive and 94 seronegative cases as examples of the same disease.

Shubert *et al.* (1954), reporting upon 27 patients Paul-Bunnell negative but otherwise satisfying the clinical and haematological qualifications for a diagnosis of infectious mononucleosis, considered these cases "to be examples of a different disease, although closely allied to infectious mononucleosis." Disinclined to employ the term "seronegative infectious mononucleosis" because seronegativity was not the only feature differentiating this from the seropositive disease, the term "epidemic variant of infectious mononucleosis" was adopted.

These three viewpoints among many are representative of the difficulty of finding a satisfactory terminology.

The present field study supports the main contention of Shubert *et al.* that seronegative cases should be regarded as examples of a *different disease*. The characteristics which they selected as points of differentiation between seropositive and seronegative disease with their limited series of cases are not substantiated by the present study, but other characteristics appear to provide even more striking evidence. Thus, Shubert *et al.* considered that there were notable differences between the two disease states as regards the incidence of pyrexia, sore throat, and rashes, but this is not supported by the present study. Nor is the contention supported that in the seropositive disease lymphocytes exceed 50% of the total white cell count, whereas in the seronegative disease they tend to be less than 50% of the total count.

From the clinical standpoint, the really notable features have been set out in Table XV—namely, unequivocal differences in the age, sex, and seasonal incidence of the two diseases, and as regards laboratory findings the fact that the rate of disappearance of G.F. cells from the peripheral blood distinguishes the two diseases.

If the adjective "infectious" is employed, it is clear that the attribute of infectivity is a feeble characteristic of each disease state, but is more highly developed in the seronegative disease than in the seropositive.

Summary

Over a period of 30 months, 498 cases suspected on clinical grounds to be cases of glandular fever were found to comprise 242 cases Paul-Bunnell positive, 100 cases Paul-Bunnell negative and haematologically positive, and 156 cases due to other diseases.

On purely clinical grounds it has not been possible to distinguish seropositive cases from seronegative cases other than in retrospect: seropositive cases tend to be the more severe.

There were notable differences in the seasonal trends and in the age and sex incidence of the two disease states.

The infectivity of either disease state was low, but the seronegative disease appeared to be the more infectious.

Average data are presented about the duration of the positive Paul-Bunnell reaction and the associated presence of G.F. cells in the peripheral blood film.

A positive Paul-Bunnell reaction is found approximately twice as long as G.F. cells in the peripheral blood film.

A doubtful positive Paul-Bunnell reaction, too weak to titrate, has been found to be significant and associated either with an incipient phase or, more usually, a regressive phase of the seropositive disease.

In seropositive cases the G.F. cells are present in significant numbers in the peripheral blood film approximately twice as long as in seronegative cases.

We gratefully acknowledge the assistance of the members of the Glandular Fever Committee, of the hospital laboratory services, of the general practitioners, of the C.O. Military Hospital, Wheatley, and particularly of Dr. Rosemary Biggs, who collaborated in the collection of data for this field study.

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ACUTE APPENDICITIS

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The number of deaths resulting from acute appendicitis in England and Wales was remarkably constant for the years 1935 to 1938, the successive annual totals being 3,178, 3,052, 3,039, and 3,027. By 1944 the number of deaths had fallen to 1,881, and since then the steady decline in mortality has been maintained, the comparable total for 1954 being 969 (Registrar-General, 1935-8, 1944, 1954). The major factor in bringing about this fall in mortality has been the advance in the treatment of peritonitis. It is generally accepted that further reduction in the mortality will be achieved only if earlier diagnosis allows surgical intervention before the onset of complications due to the spread of infection beyond the appendix.

Recent articles on appendicitis have focused attention on treatment, and we thought that a study with emphasis on diagnosis might be of value. Few problems of diagnosis present more difficulty to the general practitioner or surgeon, and one of the main difficulties is caused by the frequency with which the onset and clinical features are atypical, especially in the very young and very old patient. As with acute pancreatitis, the greatest aid to diagnosis of appendicitis is a constant awareness of its possibility.

Material

The 549 patients who form the material for this study were admitted to one surgical charge of the Royal Infirmary of Edinburgh over a period of three years (1953-6), and in all of them the diagnosis of acute appendicitis was proved at operation. Most of the patients comprising the series were operated on by one surgeon and the remainder were under his close supervision, so that the indications for operation, the classification of the operative findings, and the operative and post-operative treatment were uniform throughout. None of the patients was treated conservatively.

Classification of Patients.—We have adopted a modified form of the simple classification used by Gilmour and Lowdon (1952), Rees (1952), and Wolff and Hindman (1952) (Table I). In our series 80% of patients were operated on

TABLE I.—Classification

Group	Condition	No. of Patients
1	Acute appendicitis	441 (80.3%)
2	Acute perforated appendicitis with localized peritonitis	25 (4.5%)
3	Acute perforated appendicitis with abscess formation	39 (7.1%)
4	Acute perforated appendicitis with generalized peritonitis	44 (8.1%)
	Total	549 (100%)

before the infection had spread beyond the appendix. In the remaining 20% infection had spread to such an extent that drainage of the area was necessary.

Age and Sex Incidence (Table II).—None of the patients in this series was under the age of 12 years; 64% were under 30 years of age and only 5% were 60 or more. Table III shows that with advancing age the percentage of patients with simple acute appendicitis diminishes whereas the percentage with perforated appendicitis increases. For example, the ratio of complicated to simple appendicitis was 1:8 in the second decade, 1:2 in the fifth decade, and 3:2 in patients of 60 and over.