GLANDULAR FEVER, now known as infectious mononucleosis (I.M.), was described in children by Pfeiffer of Wiesbaden in 1889. Byers (1904) wrote of 33 cases in Northern Ireland, which occurred in the age group thirteen months to twenty-five years. An epidemic in a children’s ward in Baltimore was reported by Burns (1909). The condition was well reviewed by Tidy and Morley (1921); and in 1923 Tidy and Daniel came to the conclusion that glandular fever was a clinical entity, an absolute lymphocytosis was usual and that it was the same condition described as ‘infective mononucleosis’.

A notable advance in diagnosis was made by Paul and Bunnell (1932), who found high concentrations of heterophil antibodies, in the form of sheep cell agglutinins, in the active stages of I.M. Since then important modifications by Davidsohn and Walker (1935) and Davidsohn (1937) have led to the development of the more accurate differential absorption test where the antibodies in I.M. are not removed by titration with guinea-pig kidney. In recent years a rapid slide test, using a suspension of horse erythrocytes as the antigen, has been shown to have a high degree of specificity (Hoff and Bauer, 1965, and Davidson, 1967).

CLINICAL PICTURE

Seventy-one per cent of cases of I.M. occur between the ages of fifteen and thirty years (Newell, 1957). The incubation period is uncertain and Pullen (1973) surmised 7 to 49 days. A variety of non-specific symptoms such as malaise, headache and anorexia may appear as initial features, but the most characteristic complaint is of sore throat accounted for by a mild to moderate pharyngitis.
Virtually all patients develop a variable fever. Cervical lymphadenopathy, often accompanied by axillary and inguinal lymphadenopathy, is usually present by the end of the first week and slight splenomegaly may be detected in fifty percent of patients during the second week. Although most show some derangement of liver function only a few develop overt jaundice or hepatomegaly.

The disease follows a benign course as a rule and two-thirds appear to be fully recovered by the third week. Few, in this country, are admitted to hospital. A small number develop complications during the course of the illness and it is in this group that occasional fatalities are noted. In a critical review of fatal cases Penman (1970) pointed out the lack of proof of I.M. in some reports: he came to the conclusion that the mortality rate is “probably less than 1 per 3,000 cases”. He grouped the reported causes of death as splenic rupture, neurological complications (excluding cerebral haemorrhage), respiratory obstruction, secondary infection, liver failure and miscellaneous. Other published fatal cases include those of Ainley (1949), Shinton and Hawkins (1956). Dawson and Dowling (1962), Harries and Ferguson (1968), and Jain and Sherlock (1975).

In the present series no fatalities have come to our notice.

NOTIFICATION
I.M. is statutorily notifiable in Eire, but not in England or Scotland. It was previously notifiable in Northern Ireland, from 1949 to mid-1968, but this is no longer required.

AETIOLOGY
Evidence points to a virus as the cause, probably the herpes-like virus found in cultures of cells derived from Burkitt’s lymphoma (Epstein et al., 1964), but this remains unproven. The virus (now known as the Epstein-Barr virus or EBV) may be a latent “passenger” virus activated by I.M. rather than the true aetiological agent (Lancet, 1968). Investigations have continued and Henle and Henle (1973) consider that there is now no doubt that the EB virus is the cause of I.M., although one of Koch’s postulates remains unfulfilled.

MODE OF INFECTION
Despite records of “epidemics” since the turn of the century clearly many cases were not patients with I.M. Not until the advent of the Paul-Bunnell test and its later modifications could an accurate diagnosis be made. However, although apparently not highly infectious, outbreaks within families are not rare. Although not all cases were proved, Klaber and Lacey (1968) reported an epidemic involving 75 patients in a rural practice. Thirteen families had “two or more cases” and in six families three or four members were involved.

In Dameshek’s view (1969) I.M. appears to be an individual infection and it has been suggested by several authors that intimate oral contact, with consequent salivary exchange, is the likely mode of infection (Hoagland, 1955, Odegaard, 1967). Indeed, it is often referred to as “the kissing disease”.

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Solem and Jørgensen (1969) reported a rare mode of infection—the third case of transmission of the disease by blood transfusion. The donor developed proved I.M. two days after giving the blood and the recipient three weeks after receiving it.

CRITERIA FOR DIAGNOSIS

Ideally the triad of a clinical picture of I.M., a diagnostic heterophil antibody (Paul-Bunnell) titre and typical blood count findings should be present. For the purpose of the present survey an absorbed Paul-Bunnell titre of 1 in 56 at some time during the course of the illness was required, plus blood count findings of an absolute or relative lymphocytosis, with atypical mononuclear cells in the blood film. Because few of the patients were seen by us and because we have frequently had to rely on the clinical summary provided with the specimens the importance of the clinical picture has not been stressed in the selection of cases.

In this paper the heterophil antibody procedure is referred to as the "Paul-Bunnell" test or titre.

SEROLOGICAL TECHNIQUES

Since about 1967 all sera for Paul-Bunnell tests have been screened with the 'Denco'-I.M. slide test. Negative results are reported as "Paul-Bunnell negative": sera giving a positive result have been further tested by the full three-row differential agglutination technique described by Davidsohn (1937) using Wellcome Reagents guinea-pig kidney and ox red cell suspensions for the absorption procedures. Titres of 1 in 56 or greater after guinea-pig kidney absorption have been regarded as diagnostic of I.M.: lower titres are reported as "suggestive" and repeat specimens requested.

Recently Wellcome Reagents have ceased to produce their guinea-pig kidney and ox red cell reagents. Therefore since late 1975 the absorption tests have been omitted; the 'Denco'-I.M. slide test is done instead and, if positive, is followed by a single row titration against sheep cells.

SOURCE OF SPECIMENS

The material analysed was collected over seven years (Sept. 1969 to Aug. 1976) from specimens submitted to The Laboratories, Belfast City Hospital. Eighty-six per cent were referred initially by general practitioners and fourteen per cent from hospital doctors. The 465 cases came from a cross-section of the general public and not as in some surveys from selected groups such as army personnel or university students.

1 Denver Chemical Manufacturing Co., Stamford, Conn., U.S.A.

2 Wellcome Reagents Ltd., 299-303 Hither Green Lane, Hither Green, London SE13 6TJ.
ANALYSIS OF RESULTS

No accurate incidence of I.M. in the population can be assessed because it is not nationally notifiable, some patients are never diagnosed and some do not consult their doctors. Where strict diagnostic standards have been applied Penman (1966) found the overall incidence in the Portsmouth area in 1962-63 to be 38 per 100,000 population "...an average of one case annually in a medium-sized general practice". Despite what was considered a conservative estimate this is about five times the 1962 figure in Northern Ireland of only 7.7 per 100,000—and at a time there when I.M. was statutorily notifiable.

AGE AND SEX INCIDENCE

Results in the current series in Northern Ireland are shown in Table 1.

| Ages last Birthday | Males | Females | Total | Approx. % |
|--------------------|-------|---------|-------|-----------|
| Below 11           | 29    | 23      | 52    | 11        |
| 11—15              | 38    | 58      | 96    | 21        |
| 16—20              | 65    | 109     | 174   | 37        |
| 21—25              | 46    | 33      | 79    | 17        |
| 26—30              | 24    | 7       | 31    | 7         |
| 31—35              | 1     | 6       | 7     | 2         |
| 36—40              | 4     | 2       | 6     | 1         |
| 41—45              | 3     | 3       | 6     | 1         |
| 46—50              | 0     | 0       | 0     | 0         |
| 51—60              | 3     | 1       | 4     | 1         |
| Age unknown        | 5     | 5       | 10    | 2         |
| Total              | 218 males | 247 females | (47%) | (53%)     |

It is of interest that Hoagland (1955) and Penman (1966) found that I.M. was uncommon in children, which contrasts with results in the present series where it will be seen that nearly a third were under the age of sixteen, with about 23 per cent less than fourteen years. The youngest was aged four years. The highest incidence (37 per cent) was in the sixteen to twenty age group, while between sixteen and thirty years 61 per cent developed the condition. There was one in his sixtieth year: "very few" over sixty have been described. Finch (1969) and Corr (1967) could only report eight substantiated cases in the literature. It was perhaps surprising that no patients in the 46-50 age group were affected.

MONTHLY INCIDENCE

The Public Health Laboratory Service (1972) received reports of 7,479 cases of I.M. in 1971 in the British Isles: of these over 3,000 were recorded in the
three-and-a-half months between mid-February and the beginning of June. This source also points out that the continuing increase in the number of serologically proved cases may, in part, be due to the growing popularity of the simple slide agglutination test. Dunnet (1963), in an analysis of eighty cases, noted a peak incidence in February. However, in the present series we were unable to detect any significant seasonal variation (Table II).

**Table II**

*Incidence in the Four Seasons*

| Seasons               | Cases | Per Cent |
|-----------------------|-------|----------|
| Winter (Dec. - Feb.)  | 113   | 24.3     |
| Spring (Mar. - May)   | 120   | 25.8     |
| Summer (June - Aug.)  | 109   | 23.4     |
| Autumn (Sept. - Nov.) | 123   | 26.5     |
| **TOTAL = 465**       |       |          |

In numerical order the four leading months were June, November, March and May, with fifty-four, forty-nine, forty-eight and forty cases respectively.

**Blood Picture**

Except for the first fifteen months of the survey blood counts were done on the Coulter³ automatic blood cell counter, Model S.

Normal ranges for haemoglobin and leucocytes were taken as follows: Haemoglobin (g/dl): male adults 13.5 - 18.0; female adults 11.5 - 16.5; children (under 15) 12.5. Leucocytes (10⁹/l 4.0 - 11.0 (adults).

**Haemoglobin Levels**

Anaemia is reported to be not uncommon in I.M. and is usually slight: where it is marked it results either from acute haemolysis or bleeding secondary to thrombocytopenia. Samples were available from 465 patients comprising 155 adult males, 179 adult females, and 121 children under the age of fifteen: 27 adult males and 13 adult females were anaemic and 43 children. This represented, respectively, anaemia in 17, 7 and 36 per cent—figures which are probably less than the true incidence. The lowest haemoglobin levels (g/dl) were: adult male 11.1, adult female 10.6; and child 10.6.

**Total Leucocyte Count**

White cell counts were carried out on all patients. Because there is uncertainty about the upper normal limit of the total white cell count in children those under the age of fourteen years have been excluded from 'a'.

³ Coulter Electronics Ltd., Cold Harbour Lane, Harpenden, Herts. AL5 4UN.
(a) **Above** $11.0 \times 10^9/1$. 70 males (45%) and 59 females (33%) fell into this category. The highest figure was $28.1 \times 10^9/1$. None showed a polymorphonuclear leucocytosis, which is thought occasionally to occur in the early stages (Tidy, 1952, Emond, 1968, de Gruchy, 1970, Smith, 1972).

(b) **Below** $4.0 \times 10^9/1$. Only 3 patients out of 465 had a leucopenia, the lowest count being $2.6 \times 10^9/1$. Their ages were 13, 15 and 16 years. This is in contrast to Dunnet (1963) who found leucopenia in the first few days of illness more usual than a leucocytosis.

**Differential Leucocyte Count**

As previously mentioned an absolute or relative lymphocytosis, with atypical mononuclear cells, was essential to the diagnostic triad. The percentage of atypical mononuclear cells was not routinely calculated.

**Platelet Count**

Too few were carried out for an assessment. Marked thrombocytopenia is rare, but about 50 per cent of cases show some degree of thrombocytopenia during the first four weeks of illness (Carter, 1965).

**Eosinophil Count**

Nine patients (2%) had an eosinophilia (more than $0.44 \times 10^9/1$) in the first blood count. Smith (1972) stated that eosinophilia is more common during convalescence.

**HETEROPHIL ANTIBODY TITRES AFTER ABSORPTION WITH GUINEA-PIG KIDNEY (G.P.K.) SUSPENSION**

These positive Paul-Bunnell results were obtained from the first positive sample of clotted blood received. (Table III).

| Titre  | Number of patients | Percentage |
|--------|--------------------|------------|
| 1: 56  | 87                 | 18.7       |
| 1: 112 | 131                | 28.2       |
| 1: 224 | 83                 | 17.8       |
| 1: 448 | 78                 | 16.8       |
| 1: 896 | 39                 | 8.4        |
| 1: 1792| 24                 | 5.2        |
| 1: 3784| 14                 | 3.0        |
| 1: 7168| 6                  | 1.3        |
| 1: 14336| 2               | 0.4        |
| 1: 14336| 1               | 0.2        |

**TOTAL** = 465
It is almost certainly true that the Paul-Bunnell titre does not reflect the stage or severity of the disease (Librach, 1961). In the current series of 465 patients full follow-up was not always achieved and must at times have failed to demonstrate the diagnostic value of a rising titre in some cases. In fact 27 originally non-diagnostic titres became diagnostically positive within three weeks when the test was repeated.

It is of interest that the longest period an absorbed Paul-Bunnell titre was held at the diagnostic level of 1 in 56 or higher was twenty weeks. Titres of this order tended to disappear after about four weeks.

HAEMOLYTIC ANAEMIA: ANTI-i SPECIFICITY: ANTI GLOBULIN (COOMBS') TEST

When haemolytic anaemia occurs it is frequently associated with cold agglutinins of anti-i specificity. However, Jenkins et al. (1965) tested sera from 85 patients with uncomplicated I.M. and found weak anti-i agglutinins in about 8 per cent of cases. Hossaini (1970), on the other hand, reported the incidence of anti-i agglutinins to be 69.2 per cent in 52 patients in uncomplicated I.M. It is evidently only in those who develop antibody of sufficient titre or thermal amplitude that overt haemolysis appears. The direct Coombs' test may be positive in association with the presence of anti-i, but anti-i tests were rarely performed in the current survey.

Following a probable case of I.M. complicated by haemolytic anaemia screening of all proved I.M. cases was started in September 1970. Coombs' tests were carried out on 624 first and follow-up samples. In seventeen patients (3.7 per cent) the direct Coombs' test was found to be positive. To our knowledge in none was there clinical evidence of haemolytic anaemia, although it must be conceded that there was no opportunity to screen patients routinely for occult haemolysis.

The haemoglobin levels in the seventeen Coombs'-positive cases ranged from 11.1 g/dl to 17.8 g/dl. Therefore, judged by these initial tests and clinical evidence, no frank haemolytic anaemia developed. Where Coombs' tests were repeated the evidence was that positive results became negative in a matter of days although the Paul-Bunnell test remained positive.

RELAPSES OR FRESH INFECTIONS

Kaufman (1950) and Tidy (1952) considered that relapses or recurrences were by no means rare. Bender (1962) reported a recurrence in a student four-and-a-half years after the initial attack. On the other hand, Rose (1972), with extensive experience of I.M. in a university population, stated that he had never seen a bona fide recurrence. Similarly Edmunds (1972), usually with two to three years follow-up study, never encountered a recurrence. Smith (1972) thought that there were unquestionable recurrences, but that they were "extremely rare".

Bearing in mind that "false positive" seriological reactions are reported in association with conditions other than I.M. the question of a genuine relapse or
fresh infection was carefully considered. However, in the current survey neither of these diagnoses could be substantiated despite suspicion on clinical grounds on some occasions.

FAMILY INFECTIONS

Epidemics and outbreaks of I.M. in families have already been mentioned. No outbreaks of epidemic proportions were encountered in the present series, but four families are known to have had more than one member infected within a short period. One family had three members affected from mid-March to the 1st June. Two from each of the three other families were affected and the period between infections varied from one to eleven weeks. Two other families had two members almost certainly affected, but insufficient tests were carried out to enable them to be included in the series.

A SEPARATE “DOUBTFUL” CATEGORY

Not included in the present series are 160 additional cases (116 with diagnostically positive Paul-Bunnell titres) where I.M. was probable but the diagnostic criteria could not be met. Sometimes the clinical picture was suggestive, but either the haematological findings or negative or low titre serological results were not in agreement; or occasionally diagnostically positive Paul-Bunnell results were inconsistent with other findings.

Anyone dealing with I.M. is well aware that this category of “false positive” serological reactions exists, while, on the other hand, in some true cases the Paul-Bunnell test remains negative throughout. Indeed, one stimulus to starting this seven year survey was the unusual case in general practice some years before of a young girl with I.M. who almost certainly transmitted it to her grandfather. He acknowledged kissing her on the mouth on many occasions during the incubation period. He developed the clinical picture of I.M., but unfortunately the only specimen sent to the laboratory was for a Paul-Bunnell test, which was diagnostically positive.

The following three cases, not of I.M., are examples of false positive Paul-Bunnell reactions.

1. Girl (10 years), in the care of Dr. C. M. B. Field, who presented with idiopathic thrombocytopenic purpura, twice had an absorbed Paul-Bunnell titre of 1 in 56 and once a titre of 1 in 28. Blood films on five different occasions and bone marrow aspirate were not suggestive of I.M.

2. Another patient (20 years), in early pregnancy, recorded an absorbed Paul-Bunnell titre which varied from 1 in 56 to 1 in 448 over a six week period, with normal blood films. At fifteen weeks gestation she was shown to have a rubella infection.

3. A female (24 years), thirty-two weeks pregnant, presented with a marked megaloblastic anaemia, sore throat, epistaxis and urinary infection. The absorbed Paul-Bunnell titre was 1 in 112, but blood and bone marrow films were not suggestive of I.M.; nor had the husband been affected.
An example of a "false negative" serological test was the case of a 19-year-old male student, with clinical and haematological findings consistent with I.M., who developed an auto-immune haemolytic anaemia with anti-i specificity. The I.M. slide test was weakly positive on two occasions but the Paul-Bunnell remained negative.

Hobson et al. (1958) also gave figures in their survey for a separate group of 100 patients whose diagnosis was in doubt. They were suspected clinically of having "glandular fever", and although haematologically typical they remained Paul-Bunnell negative.

SUMMARY

A total of 465 cases of infectious mononucleosis in Northern Ireland with characteristic haematological and serological findings and presenting over a seven-year period (1969-1976) are reviewed. The history, clinical findings, aetiology and epidemiology of the condition are discussed.

Nearly a third of 465 patients were under sixteen years with sixty-one per cent presenting between the ages of sixteen and thirty. Despite occasional reports to the contrary no significant variation in seasonal incidence was recorded. Seventeen patients had a positive direct Coombs' test though in none of these was there evidence of frank haemolysis; repeat testing showed that the positive results became negative in a matter days. Four families were noted to have more than one infected member within a short period. No report of a fatal outcome in any of the 465 cases was noted.

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