BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 9 1943

INFECTIOUS MONONUCLEOSIS

WITH AN ACCOUNT OF AN EPIDEMIC IN AN E.M.S. HOSPITAL

BY

JAMES P. A. HALCROW, M.B., M.R.C.P.Ed., D.P.H.

Resident Physician

LLOYD M. OWEN, M.B., Ch.B.

Ex-Resident Medical Officer

AND

NORMAN O. RODGER, M.B., Ch.B.

Medical Registrar

Emergency Medical Service, Scotland

In August, 1942, an epidemic of infectious mononucleosis, presenting some unusual features, was discovered in an E.M.S. hospital, and was also apparently widespread in surrounding districts. During the past few years interest in infectious mononucleosis has increased and many articles have been published. The condition was reviewed in a most comprehensive manner by Bernstein in 1940 and again by Smeall in 1942. Paul and Bunnell, by their discovery in 1932 that the serum of patients with this disease contains an antibody which agglutinates sheep's red cells in high dilution, did much to establish it as a separate entity. The disease may vary in severity from cases with symptoms so mild as to pass unrecognized to an acute illness with severe sore throat, glandular enlargement, and pyrexia, followed by a long period of debility and frequent exacerbations.

Diagnosis

The clinical manifestations are protean, and diagnosis on clinical grounds alone may be almost impossible; examination of a blood smear and a Paul-Bunnell test, however, will soon confirm diagnosis. Tidy, in his papers on this subject, has dealt thoroughly with the clinical manifestations. He subdivides the disease into three groups—anginose, glandular, and febrile types. In the glandular type the onset is usually characterized by slight pyrexia, frontal headaches, and pain and stiffness at the back of the neck. The first glands to be enlarged are usually those in the posterior triangles, often on the left side, and later all other groups of glands may be involved. Glandular enlargement may persist for many months after all other symptoms have disappeared. Tidy states that in about half the cases the spleen is also involved. The anginose type may closely simulate severe acute tonsillitis or diphtheria. Vincent's organisms are often the predominant flora obtained from the throat. The febrile type occurs more commonly in adults, and is characterized by a fairly sharp onset with severe frontal headache and stiffness of the neck. Rashes may occur with this type and may raise the suspicion of typhoid fever, especially if there is splenic enlargement (Tidy, 1934). Morbilliform and scarlatiniform rashes also occur. In this type, glandular enlargement may not be present until late in the disease and toxæmia and weakness may be prominent features. With all three types various complications may arise: red cells and albumin may be found in the urine; epistaxis and purpuric eruptions have been described (Downey and McKinlay, 1923). In some cases the symptoms referable to the central

nervous system may be so severe as to simulate meningitis, and in some there is an increased cell count in the C.S.F. with definite meningitic signs. These cases may closely simulate acute lymphocytic meningitis—here again the Paul-Bunnell test is of great value in differentiation.

Jaundice has been described in infectious mononucleosis, and in these cases catarrhal jaundice may be closely simulated, especially as the blood pictures are not unlike. Bernstein suggests that some cases of catarrhal jaundice with enlarged spleens are probably cases of infectious mononucleosis.

Serological Diagnosis

The Paul-Bunnell reaction is of great value in establishing the diagnosis of infectious mononucleosis. There is, however, much dispute in the literature regarding the titre which can be accepted as diagnostic of the condition. Tidy (1939) regards a titre of 1:64 as specific, but other writers do not accept a titre of less than 1:256 unless the absorption test is also positive. Paul in 1941 stated that a titre of 1:64 is nearly always of diagnostic value, while a titre of 1:32 is suggestive of it. Smeall (1942) gives the results of Paul-Bunnell tests performed on 765 patients not suffering from infectious mononucleosis or serum sickness; in 66.8% of these no agglutination was observed, while only 0.4% gave a titre of 1:64. Barrett in 1941 tested the sera of 100 normal healthy people and found only 4 with a titre of 1:40; none exceeded this figure. Paul and Bunnell in their original work found that 273 control cases gave only low titres. The Paul-Bunnell test may become positive very early in the disease, but in some cases a positive result is not obtained for three to four weeks. In view of this it is essential that in a suspected case of infectious mononucleosis repeated Paul-Bunnell tests be done, as a single negative reaction does not rule out this diagnosis. In cases with a low titre the absorption test is useful to distinguish the infectious-mononucleosis antibody. It has been found that sera from cases of infectious mononucleosis contain antibodies which are absorbed by ox cells but not by guinea-pig kidney. Sheep-cell agglutinins occurring in serum from normal people are absorbed by guinea-pig kidney but not by ox cells, while the agglutinins found in the sera of cases treated with horse serum are absorbed by both the ox cells and the guinea-pig kidney (Barrett, 1941).

In cases of infectious mononucleosis in which the Paul-Bunnell titre does not rise above 1:32 this absorption test is of great value. The Paul-Bunnell reaction may remain positive for many weeks after clinical manifestations of the disease have disappeared.

The Blood Picture

Great care in the study of blood films is necessary in establishing a diagnosis of infectious mononucleosis. It is well known that the characteristic finding is a relative and absolute increase of the lymphocytic series of cells. Tidy (1934) states that the total white count ranges between 6,000 and 15,000 per c.mm.; in many instances, however, the count has greatly exceeded this figure. Rarely, the disease may be ushered in by a leucopenia. Paul (1939) noted that in about half his cases leucopenia was a feature. Tidy mentions that the polynuclear cells often show a shift to the left, and he draws attention to the statement that the eosinophils may be low or absent during the acute stage and increased above normal during convalescence. Tidy also mentions the initial polynucleosis at the onset of the disease. It is, however, in the mononuclear cells that striking changes occur: these cells often constitute 60% and upwards of the total white count (Bernstein, 1940). Bernstein comments on the fact that mononucleosis occurs more commonly in sporadic cases than in the epidemics, and he attributes this to the fact that only the more obvious cases of the sporadic type are recognized, while in a known epidemic slight changes in the blood are looked for and found.

The mononuclear cells in infectious mononucleosis may be divided into three groups: Group 1, normal lymphocytes; Group 2, monocytes; Group 3, abnormal or atypical lymphocytes. Groups 1 and 2 correspond to cells found in normal blood. The atypical lymphocytes show great variation in morphology; they vary in size and shape, and the nucleus may be oval, indented, or show lobulation. Nuclear chromatin often shows fenestration. Downey in 1923 divided abnormal lymphocytes into three types: Type 1 corresponds to the cell described above, and in Type 2 cells the chromatin of the nucleus is not so condensed and the cytoplasm does not show vacuolation; Type 3 cells resemble those of acute lymphatic leukaemia, the nucleus possessing nucleoli and a basophilic cytoplasm. It is generally agreed that the erythrocytes and the platelets are not affected in infectious mononucleosis, and bleeding and coagulation times are normal. The blood picture typical of infectious mononucleosis is characterized by a relative and absolute lymphocytosis and the presence of abnormal lymphocytes.

Many writers describe cases of infectious mononucleosis in which serological tests for syphilis have been positive. Bernstein states that 18% of his cases were serologically positive for syphilis, while Radford and Rolleston drew attention to this phenomenon in 1930. Paul in 1939 described several cases in which a positive Wassermann reaction was obtained. Kahn in 1939 drew attention to the fact that these false positive serological tests for syphilis may persist for several months.

The Marrow

Freeman in 1936 found an increase in lymphocytes and sometimes a slight shift to the left of the myeloid leucocytes in marrow from cases of infectious mononucleosis. Israëls in 1941 found, in a few cases he examined, that the marrow showed an increase in plasma cells and abnormal lymphocytes: Vogel and Bassen in 1939, however, in four cases found no change in the marrow. Sternal puncture would certainly help to differentiate between acute lymphatic leukaemia and infectious mononucleosis.

Pathology of Lymph Glands

All authors agree that there is marked hyperplasia of lymphoid and reticulo-endothelial cells. Pratt in 1931 described great hyperplasia of the reticulo-endothelial cells. Downey and Stasney referred to similar pathological findings in 1936. Longcope in 1922 gave an essentially similar picture. The gland architecture is maintained, and the abnormal lymphocytes found in peripheral blood can be demonstrated throughout the glands (Gall and Stout, 1940).

The changes found in lymph glands are not diagnostic, and could be confused with any non-specific adenitis, although biopsy of a lymph gland would readily differentiate between infectious mononucleosis and more serious conditions such as lymphatic leukaemia and lymphadenoma.

Most epidemics of infectious mononucleosis have occurred among children. Tidy and Morley (1921) reckoned that 85%

of epidemic cases of this disease occurred in children under 12 years of age. Nolan in 1935 described an epidemic resembling infectious mononucleosis in which only 5 cases out of 220 were in adults. The Paul-Bunnell titres in his cases ranged from 1:80 to 1:320, and most of the cases appeared to be mild. Most epidemics of infectious mononucleosis have occurred in hospitals and institutions. The incubation period usually varies from 5 to 11 days. Boyd (1940) states that studies of apparently healthy medical students during an epidemic show that many mild cases probably pass undiagnosed. Reversbach and Lenert (1941) describe 16 cases among 108 children who were receiving convalescent treatment after rheumatic fever. None of these 16 cases showed symptoms or signs; the blood picture was apparently typical, although the predominating cell was the small lymphocyte and the Paul-Bunnell reaction was negative. Smith (1941) describes leucocytosis with absolute lymphocytosis occurring in children without symptoms or signs of disease being manifest.

Description of the Epidemic

The epidemic described below differs in many respects from those previously recorded. The age incidence was from 20 to 45 years; the outbreak occurred in a selected population, mainly young soldiers who, although in hospital, were relatively fit. The disease was distributed equally between males and females. Two older cases may be specially mentioned here: one was that of a woman aged 84 who had no clinical manifestations of the disease, but had a Paul-Bunnell reaction of 1:128 and a mononucleosis of 65%; the other was that of a woman aged 64 who had no clinical manifestations, a negative Paul-Bunnell reaction, but a very typical blood picture with a mononucleosis of 48%. These patients were the oldest observed. The incubation period in our cases varied from 5 to 10 days; in one instance it was exactly 5 days.

The most interesting feature of the epidemic was the occurrence of cases without clinical manifestations. In many instances the Paul-Bunnell antibody was present along with the typical blood changes—i.e., a relative and absolute mononucleosis with abnormal lymphocytes present in the peripheral blood—but clinical manifestations were completely lacking.

The first case to be detected in this outbreak was that of a woman aged 25, admitted to the hospital on Aug. 5, 1942, with a typical attack of severe anginose infectious mononucleosis. She had a mononucleosis of 83% and her Paul-Bunnell reaction was positive at 1:340. Four other cases were also admitted to the medical unit early in August. On Aug. 12 one of the male medical staff who was in close attendance on the first patient began to suffer from symptoms of the disease, although he made no special comment until Aug. 23, when he had generalized glandular enlargement. From Aug. 12 onwards many members of the nursing and medical staff began to suffer from moderately severe symptoms of infectious mononucleosis, and cases also occurred among the other patients. As the infection seemed to be widespread, blood films were examined from all patients in the unit at this time, with the astonishing result that every one was found to have a blood picture typical of infectious mononucleosis, although many were symptom-free. On Aug. 26 it was decided to take sample blood films from wards in other units of the hospital, and these again showed a blood picture typical of the disease. As a great number of the staff and patients were now complaining of symptoms it was decided to close the hospital to admissions from Aug. 28, and a thorough investigation was made into the outbreak. At this time 273 patients in the hospital were examined clinically for symptoms and signs of infectious mononucleosis and, so far as time permitted, serial Paul-Bunnell tests were done, together with blood examinations. In addition, members of the medical and nursing staffs were investigated, making the total 296. The result revealed that 97.9% of those investigated showed evidence of the infection. In only 6 instances could the infection be completely excluded; these presented no symptoms or signs and had normal blood pictures with low titres or negative Paul-Bunnell reactions. Of the 296 persons investigated at this time 125 were clinical cases of infectious mononucleosis, and 165 had blood and serological changes but no clinical manifestations of the disease. In addition, relatives of the medical and nursing staffs living outside the hospital developed clinical manifestations of the disease which were quite well marked. Previous epidemics of infectious mononucleosis have been described, but none appears to have reached the high percentage of positive cases present in this epidemic. It would seem that the infectivity was very high, or else the hospital and surrounding districts were subjected to a very heavy dosage, perhaps due to black-out conditions.

Cases can be subdivided into groups according to the highest titre of the Paul-Bunnell test.

TABLE I.—296 Cases, plus 23 in which no Paul-Bunnell Tests were Done

Distribution of Cases	Paul-Bunnell End Titre						Paul-Bunnell not Done, but Blood Picture Typical
	1:512	1:256	1:128	1:64	1:32	Negative at 1:32	
Medical unit ..	7	9	25	24	5	3	—
Aver. W.B.C. ..	10,900	6,600	10,900	9,400	9,900	9,900	—
.. mononuc.	49%	49%	46%	47%	44%	52%	—
Orthopaedic unit ..	4	12	34	52	49	27	20
Surgical unit ..	0	6	16	13	8	2	3
Cases with clinical manifestations ..	9	15	40	40	16	5	—
Total cases ..	11	27	75	89	62	32	23

The cases in the medical unit include members of the nursing and medical staffs. Of the six cases which were entirely negative, five were in the orthopaedic unit and one in the surgical unit. All six negative cases had Paul-Bunnell titres of 1:32 or less. In Table I 23 additional cases are shown: these cases had no Paul-Bunnell tests, but their blood pictures were characteristic. The surgical unit is closely adjacent to the medical unit, in which infection was most severe; the main part of the orthopaedic unit is 1,000 yards away from the medical unit. All the surgical staff of the surgical and orthopaedic units had clinical manifestations of the disease.

As the infection seemed widespread in the hospital it was decided to use as a control groups of cases elsewhere, and Dr. E. Neil Reid, County M.O.H., kindly gave us facilities to examine cases in centres at varying distances away. The first group—19 A.R.P. workers—examined was in a town closely adjacent. Paul-Bunnell tests, white blood counts, and differential counts were done on all of them. Of these 19 cases (Table II, Group A), 7 were in close contact with the hospital, and most of the others had opportunities to contact its personnel. A further control group (B) was examined in a town about 5 miles from the hospital, this being the place from which the first severe anginose case was admitted. Group C was drawn from an A.R.P. group in a town about 13 miles and Group D from a small country village about 20 miles from the hospital. In addition, the Department of Health for Scotland arranged for a control group (E) in another E.M.S. hospital about 35 miles distant, and we are indebted to the Department for the results shown in Table II.

TABLE II.—Results of Control Investigations

Group	No. of Cases	Paul-Bunnell Titre					Blood Picture		Clinical Manifestations	
		1:256	1:128	1:64	1:32	Negative at 1:32	Pos.	Neg.	Pos.	Neg.
A & B	37	6	12	7	8	3	37	—	2	35
C & D	35	—	1	3	10	21	4	31	2	33
E ..	20	—	—	—	—	20	—	20	—	20

Clinical Features

Clinically, cases can be divided into four groups:

1. *Latent Cases.*—Cases with a relative or an absolute mononucleosis with abnormal lymphocytes present and a positive Paul-Bunnell reaction, but in which there were no symptoms or signs of the disease.

2. *Mild Cases.*—Cases with symptoms and signs, but not so severe as to lead to abstinence from duty, or would not have done so if the patient had not already been in hospital with some other complaint.

3. *Moderate Cases.*—Similar to Group 2, but with severer symptoms and patient confined to bed for a day or two.

4. *Severe Cases.*—Patients more seriously ill, and diagnosis found difficult.

Symptomatology

Headache.—This was present in 92 cases and was severe; it was frontal in distribution, intermittent in character, and tended to recur daily for several days. Pain behind the eyes was often severe, and a mild conjunctivitis was present in a fair number of cases.

Stiff Neck.—Common, and probably due to the enlarged glands. Definite nuchal rigidity was observed in two cases.

Mental Symptoms.—These occurred in 31 cases, and consisted of slight confusion, inability to concentrate, transient forgetfulness, lassitude, and insomnia.

Pyrexia.—This was not a feature except in anginose cases. In one case pyrexia was the only feature, and continued for many days before glands became enlarged. Another glandular case had pyrexia without the illness.

Polyuria with Lumbar Pain.—Occurred in 34 cases. The urinary findings were negative except in anginose cases in which red cells and albumin were present in the urine.

Glands.—The lymphatic glands were enlarged in nearly all cases, although enlargement had sometimes to be sought for carefully. The glands were fleshy and usually tender, and the groups most frequently involved were in the posterior triangles of neck and axillae, although many cases had generalized glandular enlargement, often including the epitrochlear glands. Glandular enlargement was intermittent, with a tendency to frequent relapses. In cases from which glands were removed for biopsy it was noted that healing was very slow although no sepsis was present. In one case healing occurred only after blood transfusion, but was then rapid. Whitby and Britton (1939) state that glands should not be excised.

Spleen.—Splenic enlargement was present in about 30 cases, but many others had pain and tenderness in the left hypochondrium. In one case the spleen reached to below the umbilicus.

Rashes.—These were observed in 10 cases. (a) Maculo-papular—seen in 3 cases. In two cases the rash began between the scapulae and spread on to the front of chest and abdomen, later spreading to the upper part of arms and legs. In these two cases there was no rash on the hands, legs, or face. In the third case the rash started in the front of the body and spread round to the back and on to the flexor aspects of the arms. These three cases could have been confused with secondary syphilis, as sore throat and generalized glandular enlargement were a feature. However, the W.R. was negative, the Paul-Bunnell titre was positive at 1:256 or over, and the blood pictures were quite typical. The rashes occurred early, usually on the first or second day. (b) Scarlatiniform and morbilliform rashes were seen in the remaining 7 cases, and these rashes were very transient. (c) One case with a purpuric rash on the legs and thighs was observed.

Jaundice.—This was not seen during the epidemic, but the icteric index and the van den Bergh test, done on 15 of the severer cases, showed that 8 had latent jaundice. One case admitted after the hospital reopened had fairly severe jaundice, serum bilirubin 6 mg. per 100 c.cm., and a Paul-Bunnell titre of 1:128 with a positive absorption reaction.

Sore Throat.—Present in 35 cases. The fauces were injected, but only 4 true anginose cases were seen.

Alimentary Symptoms.—Transient diarrhoea was present in 13 cases in the early stage of the disease. Vomiting was also present, and in a few cases vomiting and diarrhoea were severe. Repeated examinations of the faeces for pathogenic organisms in these cases were negative.

Thoracic Symptoms.—Observed in many cases, and often raised the suspicion of pleurisy or pneumonia. Pain in the chest, aggravated by respiration and accompanied by cough, was the main symptom. Clinical and radiological examination of these patients was negative. It seems likely that the symptoms were due to enlarged mediastinal glands, although this was not confirmed on fluoroscopy.

Meningitic Cases.—In 5 cases meningitic symptoms were severe enough to warrant lumbar puncture. In 4 of these cases the C.S.F. pressure was high, and three of these four had a cell count above 5 per c.mm., while the one with normal cell count had an increase in protein. In the fifth case the C.S.F. was normal in every respect.

Epistaxis.—Observed in 4 cases.

One case was observed in which the salivary glands were enlarged; the blood picture was typical and the Paul-Bunnell titre 1:128. Six cases with parotid enlargement were described by Glanzmann in 1930.

In most cases the symptoms subsided completely within 5 to 21 days, but a few went on for longer periods, with relapses, and two were still having relapses after six months.

The Wassermann, Kahn, and flocculation tests were done in many cases during the epidemic and were consistently negative, irrespective of the titre of the Paul-Bunnell; thus the results differed from those obtained by other workers. In 6 cases recently observed by us in which the absorption test for the glandular fever antibody was positive, the W.R. and the flocculation test were negative throughout the course of the disease. In two of these recent cases the Paul-Bunnell titre exceeded 1:2000.

The Paul-Bunnell Test

During the first three weeks of the epidemic about 1,000 Paul-Bunnell tests were done, and in these circumstances it was impossible to put up the serum in dilutions greater than 1:512. The patients' sera were inactivated at 55° C. for 15 minutes, and dilutions of the sera ranging from 1:32 to 1:512 were set up; to these 0.5 c.cm. of 1% suspension of washed sheep red cells was added. The tubes were then placed in the incubator for one hour and afterwards left in the refrigerator all night. After shaking gently two or three times they were read by naked eye, according to the method of Paul and Bunnell. Any result about which there was the least doubt was regarded as negative. Unfortunately, at the time the epidemic was in progress it was not possible to do absorption tests to prove the presence of the true glandular fever antibody. However, one of the patients seen during the epidemic returned to hospital in the middle of December, and the Paul-Bunnell reaction on this occasion was positive 1:32, and the absorption test, using guinea-pig kidney and ox cells, was positive (Barrett, 1941). Much has been written about the diagnostic titre in the Paul-Bunnell reaction. We agree with Tidy that a titre of 1:64 is practically diagnostic. We think a titre of 1:32 is suggestive and is an indication for repetition of the test in a few days' time. In many of our cases the first two or three Paul-Bunnell tests, performed at intervals of 5 to 7 days, were negative at 1:32, and thereafter gradually rose to significant or diagnostic titres. The titres observed in this epidemic are low compared with those of sporadic cases, but are much higher than titres obtained in control groups of cases not suffering from infectious mononucleosis and described by other writers. In our series of 296 cases 202 had titres of 1:64 or over—a finding quite unlike anything previously described on controls done on normal people. It is strong evidence of the presence of some infective agent which has greatly increased the heterophile antibody response in our cases; when coupled with the clinical findings and the blood picture the evidence that the disease present was infectious mononucleosis is almost certain.

The Blood

Blood changes in infectious mononucleosis have been considered very thoroughly by various authors, and the changes found in this epidemic were much in accordance with previous descriptions.

In our series the total white count varied from 8,000 to 20,000, but only a few cases had counts of 20,000. Many had leucopenia fairly early in the disease, as found by Tidy, by Longcope, and by Davidsohn (1937). An initial polymorphonucleosis was seldom observed in this epidemic. In most of our cases the polymorphs showed a shift to the left, and stab cells were often seen; many of the polymorphs showed toxic granulation. Early in the disease we observed that eosinophils were absent; but later on, as recovery ensued, they returned in proportions greater than normal. An unusual feature was an increase in basophils, these ranging from 1 to 3% in a fairly early stage of the disease.

The platelet count and coagulation time (Lee and White) were unaffected. Anaemia was not a feature: one case of hypochromic anaemia occurred in a young adult male; this responded rapidly to iron therapy. In a female anginose case anaemia was severe and the white cells fell to 2,000, which led to a suspicion at first of agranulocytosis, especially as the abnormal cells of infectious mononucleosis have been described as occurring in agranulocytosis.

The mononucleosis varied from 45 to 60%—only in a few cases did it exceed 75%. The most striking change in the lymphocytic series of cells was the almost complete disappearance of small lymphocytes; this occurred early in the disease. The other feature was a marked increase in the numbers of large lymphocytes and the appearance of abnormal lymphocytes. Many of the large lymphocytes had a very pale cytoplasm with the typical pale nucleus of the normal large lymphocyte—in most respects they did correspond to the normal large lymphocyte except that the cytoplasm was paler than usual and often vacuolated. Many of them contained the normal reddish-purple granules in their cytoplasm. Some of the large lymphocytes appeared to be unduly fragile. Films made from early cases contained many smear cells.

The abnormal lymphocytes varied greatly in morphology—in size they ranged from a cell intermediate between a large and small lymphocyte to a large monocyte. The cytoplasm was usually much more basophilic than that of the ordinary lymphocyte and was nearly always vacuolated. Some of the abnormal cells were difficult to distinguish from plasma cells. The nuclei varied greatly in shape—some were oval or rounded, others irregular or lobulated. The nuclear chromatin was dense. Some of the abnormal lymphocytes had irregularities of their cytoplasm which resembled pseudopodia. Many of the abnormal lymphocytes seen corresponded to Downey's Type I and Type II; only in a few cases was Downey's Type III evident. Peroxidase staining failed to reveal any granules in the cytoplasm of the abnormal lymphocytes.

Blood changes usually persisted for several weeks, and a fair proportion of cases still had many abnormal cells present at the end of three months. A true monocytosis was not a notable feature; it occurred late and usually varied from 10 to 13%. An interesting phenomenon previously noted by Barrett was confirmed in this outbreak: the typical blood changes may be present before clinical manifestations make their appearance. This was noted in several cases.

In most of our cases the sedimentation rate was not affected: only in anginose cases and those with pyrexia did the B.S.R. increase. In one case with pyrexia, severe meningitic manifestations, and a C.S.F. cell count of 300 lymphocytes per c.mm. the B.S.R. never rose above 4 mm. per hour (Westergren).

Sternal puncture was performed on several cases. Examination of the marrow revealed a definite increase in lymphocytic cells and a slight increase in activity of the myeloid series of cells. In some marrow specimens there was an increase of cells of the plasma cell type, and cells resembling the abnormal lymphocyte in the peripheral blood were also noted. These findings correspond to those of Israëls (1941). It is proposed, however, to deal with the findings in a separate paper at a later date.

Pathology of Lymph Glands

Biopsy of lymph glands was performed on several cases, and reports of two, with case histories, are as follows:

Male aged 27.—Sept. 16, 1942: Sore throat and frontal headache; pain in back and axillae. Glands palpable in both axillae. During next 14 days nausea, headache, and pain in axillae and groins were present, and on Sept. 27 there was generalized glandular enlargement with slight splenomegaly. Blood examinations: Sept. 15: W.B.C. 10,600—polymorphs 70%, large lymphocytes 10%, small lymphocytes 2%, monocytes 5%, abnormal lymphocytes 13%. Sept. 23: W.B.C. 12,000—polymorphs 57%, large lymphocytes 11%, small lymphocytes 2%, eosinophils 2%, basophils 1%, monocytes 10%, abnormal lymphocytes 17%. Paul-Bunnell tests: Sept. 9, 1:64; Sept. 23, 1:128; Sept. 30, 1:128; Oct. 17, 1:32.

Report on Gland from Left Axilla.—Well-marked hyperplasia of the lymphoid tissue is present, many of the germinal centres being very large and prominent. A number of the sinusoids show moderate but distinct dilatation and are packed with numerous reticulo-endothelial mononuclear cells, together with a moderate number of small lymphocytes. Scattered areas of old fibrosis, presumably post-inflammatory, are also present.

Man aged 23.—Sickened Sept. 12, 1942, with severe frontal headache, shivering attacks, and pain in both groins. Eyes sore and watering. Glands palpable in both anterior and posterior triangles of neck and in both groins; later developed slight splenomegaly. A blood examination the same day showed: W.B.C. 18,450—polymorphs 69%, large lymphocytes 15%, small lymphocytes 2%, eosinophils 2%, basophils 1%, monocytes 1%, abnormal lymphocytes 10%. Paul-Bunnell tests: Sept. 10, 1:128; Sept. 22, 1:64; Oct. 11, 1:64.

Report on Gland from Right Groin.—Lymphoid hyperplasia is present, but is not a prominent feature. Sinusoidal dilatation is, however, much more conspicuous than in the preceding case. The dilated sinusoids contain numerous reticulo-endothelial mononuclear cells, together with a moderate number of small lymphocytes.

We are indebted to Dr. W. Forbes, Department of Pathology, Edinburgh University, for the report on these glands. The changes described in the glands correspond to previous descriptions. They cannot be regarded as specific.

Treatment

In our cases treatment was mainly symptomatic. In two anginose cases sulphapyridine was given, but no favourable

response was obtained; in fact, in one case the throat condition became worse, pyrexia continued, and blood transfusion had to be given. As the granulocytes are reduced in infectious mononucleosis and many show toxic changes, it is not surprising that sulphonamides do not give good results. Tidy (1941) states that if granulocytes are normal or increased in number no harm is done with sulphonamides. He has seen cases made worse by sulphonamides. Convalescent serum was not used. One case with fairly severe meningeal symptoms, pyrexia, and raised C.S.F. cell count made a rapid response to sulphadiazine.

Discussion

The unusual features in this epidemic were the high infectivity and the presence of latent cases. Before the epidemic started 5 known cases of infectious mononucleosis were admitted to the medical unit. This would increase the chances of spread considerably, but it hardly accounts for cases elsewhere in the hospital and outside. It seems likely that the district had an epidemic of mild infectious mononucleosis which was fairly localized. In view of the protean manifestations of the disease and the difficulty of diagnosis in the absence of haematological and serological tests the outside cases would be regarded as influenza, gastro-enteritis, etc. The difference in the findings between the outside controls near the hospital and those situated at some distance is very striking, and points to a definite localization of the disease. The spread of the epidemic within the hospital is difficult to follow. Efforts to trace case-to-case infection did not meet with any satisfactory result.

Latent cases can be explained on the basis that their immunity was sufficient to prevent the onset of clinical manifestations, as in the manner of diphtheria and meningococcus carriers. In infectious mononucleosis, however, the presence of the infecting virus produces changes in the blood picture and stimulates the production of heterophile antibodies so that latent cases are easily detected.

Differential Diagnosis

Epidemic infectious mononucleosis in adults is a relatively mild condition which simulates many other conditions. The anginose type resembles diphtheria, but here the blood picture is useful to distinguish these conditions: in diphtheria a polymorphonucleosis is invariable, while in a fully developed anginoid infectious mononucleosis absolute lymphocytosis is the rule. The cerebral type may closely simulate a true septic meningitis, but although the cell count may be raised to 300 or 400 per c.mm. the predominant cell is a small lymphocyte. This, of course, still leaves it doubtful whether or not it is a tuberculous meningitis; to exclude tuberculous meningitis the blood picture and Paul-Bunnell test are of undoubted value. In one of our cases with meningeal symptoms the C.S.F. cell count was 400 per c.mm. and optic neuritis was present for 8 weeks; the patient also had glandular enlargement, with the usual haematological and serological findings, and made a complete recovery. Cases with thoracic symptoms may simulate pleurisy or pneumonia, while those with severe vomiting and diarrhoea may closely resemble acute gastro-enteritis or typhoid fever.

The blood picture in infectious mononucleosis may be simulated to a certain extent in other conditions, particularly catarrhal jaundice and atypical pneumonia. In catarrhal jaundice abnormal lymphocytes are not infrequent, but here the Paul-Bunnell test and the absence of glandular enlargement help to differentiate the two conditions. In four cases of atypical pneumonia seen by us there was an absolute lymphocytosis, and abnormal lymphocytes were present; some of these had a deeply basophilic cytoplasm and were in many respects similar to the abnormal lymphocytes of infectious mononucleosis. However, in all four cases the Paul-Bunnell test was negative and glandular enlargement was absent. Downey and Stasney have commented on the presence of abnormal lymphocytes in agranulocytosis, a condition which may also simulate anginose infectious mononucleosis. In cases with a rash the diagnosis of secondary syphilis, rubella, or erythema nodosum may be considered. Rubella may be very difficult to differentiate from infectious mononucleosis: in both conditions the posterior triangle glands are enlarged, and the rash of

rubella may be closely simulated in infectious mononucleosis. In rubella the peripheral blood contains many Türk cells and abnormal lymphocytes, rather resembling those of infectious mononucleosis. However, the Paul-Bunnell reaction is of undoubted value, as it is consistently negative in rubella. In three cases of rubella seen by us the Paul-Bunnell test was negative throughout the disease. The rash in infectious mononucleosis may often resemble that of typhoid; and here the diagnosis may be difficult, as false positive Widal tests have been reported in infectious mononucleosis by Bernstein. Again the Paul-Bunnell test is very useful. The more serious blood disorders, such as leukaemia, should never be confused with infectious mononucleosis, for, as Smeall pointed out in 1942, the changes in the red cells in leukaemia make the distinction quite clear. In general it may be said that the diagnosis of infectious mononucleosis should not be made on any one test: the Paul-Bunnell reaction, the haematological findings, and the clinical manifestations should all be correlated before coming to a decision.

It seems likely that infectious mononucleosis, especially in a mild form, is a very common condition which can readily be mistaken for other diseases. Since the hospital reopened we have seen a number of cases of infectious mononucleosis, many of which would have been regarded as some other condition unless blood counts and Paul-Bunnell tests had been carried out.

Summary

An epidemic of infectious mononucleosis is described.

The unusual features were: (a) a high percentage of infected cases in the adult population; (b) the occurrence of cases with haematological and serological findings and no clinical manifestations; (c) the fact that blood and serological changes may precede clinical manifestations.

Attention is drawn to the difficulties in diagnosis, and the necessity for repeated Paul-Bunnell tests before excluding the disease.

The condition is always benign and does not respond favourably to sulphonamide therapy.

We are much indebted to the following for their help and advice: Prof. L. S. P. Davidson, Dr. J. L. Halliday, Prof. T. J. Mackie, Dr. A. A. F. Peel, and Dr. I. S. Sutherland; and to Dr. J. A. Jenkins, medical superintendent, and our colleagues in the hospital for their co-operation and help. We are indebted also to the Department of Health for Scotland for permission to publish this paper.

BIBLIOGRAPHY

- Barrett, A. M. (1941). *J. Hyg., Camb.*, **41**, 330.
 Bernstein, A. (1934). *J. clin. Invest.*, **13**, 419.
 — (1938). *Amer. J. med. Sci.*, **196**, 79.
 — (1940). *Medicine*, **19**, 85.
 Boyd, W. (1940). *The Pathology of Internal Diseases*, Philadelphia.
 Davidsohn, I. (1937). *J. Amer. med. Ass.*, **108**, 289.
 Downey, H., and McKinlay, C. A. (1923). *Arch. intern. Med.*, **32**, 82.
 — and Stasney, J. (1936). *Folia Haemat. Lpz.*, **87**, 417.
 Freeman, W. (1936). *Amer. J. clin. Path.*, **6**, 185.
 Gall, E. A., and Stout, H. A. (1940). *Amer. J. Path.*, **16**, 433.
 Glanzmann, E. (1930). *Das lymphoide Drüsenfieber*, Berlin.
 Israëls, M. C. G. (1941). *Lancet*, **7**, 260.
 Kahn, R. L. (1939). *Arch. Derm. Syph.*, Chicago, **39**, 92.
 Longcope, W. T. (1922). *Amer. J. med. Sci.*, **164**, 781.
 Nolan, R. A. (1935). *U.S. Nav. med. Bull.*, **33**, 479.
 Paul, J. R. (1939). *Bull. N.Y. Acad. Med.*, **15**, 43.
 — (1941). *Lancet*, **1**, 584.
 — and Bunnell, W. W. (1932). *Amer. J. med. Sci.*, **183**, 90.
 Pratt, C. L. G. (1931). *Lancet*, **2**, 794.
 Radford, M., and Rolleston, J. D. (1930). *Ibid.*, **2**, 18.
 Reysersbach, G., and Lenert, T. F. (1941). *Amer. J. Dis. Child.*, **61**, 237.
 Smeall, J. T. (1942). *Edin. med. J.*, **46**, 291.
 Smith, C. H. (1941). *Amer. J. Dis. Child.*, **62**, 231.
 Tidy, H. L. (1934). *Lancet*, **2**, 180, 236.
 — (1939). *Synopsis of Medicine*, Bristol.
 — (1941). *Lancet*, **1**, 227.
 — and Morley, E. B. (1921). *British Medical Journal*, **1**, 452.
 Vogel, P., and Bassen, F. A. (1939). *Amer. J. Dis. Child.*, **57**, 245.
 Whitby, L. E. H., and Britton, C. J. G. (1939). *Disorders of the Blood*, London.

Dr. E. H. Cluver's report for the year 1942 as Director of the South African Institute for Medical Research, Johannesburg, includes a section on war work. There has been further expansion in various branches of the Institute's activities to meet increasing military needs. Vaccines and sera produced under normal conditions for civilian requirements were wholly inadequate in quantity to cope with the special hazards to which campaigning troops are exposed. Their production had to be enormously increased and new procedures had to be introduced; for example, anti-gas-gangrene serum, not prepared locally before the war, is now being produced on a very large scale. A military Directorship of Pathology, under Dr. Cluver as honorary colonel, was set up to undertake the training of staff for the various military hospital laboratories and to supervise their equipment and running.