INFECTIOUS MONONUCLEOSIS*

BY

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Infectious mononucleosis presents a constant challenge to clinician and epidemiologist alike, and many problems surrounding this complex disease still await solution. Pfeiffer (1889) described an acute benign illness with characteristic lymphadenopathy in children which he called "glandular fever." Sprunt and Evans (1920) remarked upon the presence of atypical mononuclear cells in the peripheral blood and coined the term "infectious mononucleosis." Jaundice was first reported by Downey and McKinlay (1923) in one of their series of nine cases. Subsequent writers have stressed the frequency of liver involvement, and as more refined tests of hepatocellular damage became available it was clear that a very high percentage of cases developed hepatitis (Rennie and Wroblewski, 1957; Rosalki *et al.*, 1960).

Other organs may also be affected: heart and lungs (Wechsler *et al.*, 1946), central nervous system (Bernstein and Wolff, 1950), renal tract (Tidy and Daniel, 1923), and haemopoietic system (Dameshek, 1943). It is clear, therefore, that the condition is much more complex than envisaged in the original "glandular fever" of Pfeiffer.

Although the clinical picture suggests a virus infection, the aetiological agent has not yet been convincingly demonstrated. Many outbreaks have been reported in closed communities such as colleges, military camps, and other institutions, but the disease generally presents sporadically. The conflicting clinical and epidemiological pattern reported in different outbreaks has led to the popular view that the responsible agent is not a single virus but more probably a group of related viruses.

Eighty cases of infectious mononucleosis admitted to the department of infectious diseases, Royal Free Hospital, London, between the summer of 1959 and the autumn of 1962 have been investigated and the results are analysed in this paper. Liver function has been studied in considerable detail and the high incidence of hepatitis stressed, but other aspects of the disease have

TABLE I.—Age and Sex Distribution in 80 Cases of Infectious Mononucleosis

Age in Years	Sex		Total	Tonsillar/ Pharyngeal Exudate
	M	F		
Under 15	5	6	11	5
15-25	16	43	59	47
Over 25	5	5	10	7
Total	26	54	80	59

also been explored, and it is hoped that the findings may add something to the volume of work already published on this subject.

Season.—Cases occurred all the year round, but there was a tendency to favour spring and autumn, with a peak in February (Fig. 1).

Age and Sex.—Details are given in Table I. The anginose form predominated, and in the 15-25 age-group the incidence was as high as 80%.

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Diagnostic Criteria and Clinical Features

In a disease that characteristically presents such varied symptoms and signs it was found that final diagnosis required an assessment of clinical, haematological, and serological findings.

Clinical

Posterior cervical glands were invariably palpable. Axillary and groin glands were commonly enlarged, but the spleen was palpable in less than half the cases (Table II). Tonsillar and/or faucial injection was the rule and exudate was present in over half the cases. This was creamy, and was easily removable without bleeding: fetor was common. Faucial oedema was frequently seen—in one case severe enough to obstruct respiration. Dramatic relief followed an injection of hydrocortisone.

Respiratory Pathogens.—Nose, throat, and post-nasal swabs were taken from each patient on admission, subsequently being repeated in many instances. Pathogens were isolated in only 19 cases (24%) (Table II). Admittedly 44 patients (55%) had been given antibiotics before admission, but respiratory pathogens were still

FIG. 1.—Seasonal incidence in 80 cases of infectious mononucleosis.

present in 9 (20%) of these. Of the 36 cases not given antibiotics, only 10 (28%) had pathogens in nose, throat, or post-nasal swabs. It would therefore seem that administration of antibiotics had little if any influence on the development of secondary infection in the upper respiratory tract.

Enanthem.—Palatal lesions were seen in 33 cases (41%). These consisted mainly of petechiae, pin-point in size, most profuse along the division between the soft and hard palates. Each crop lasted 24 to 48 hours. Circular and linear red macules were also seen, often intermingled with the petechiae. The enanthem was most commonly seen in the anginose form at the height of the illness.

Exanthem.—A fine macular rash, very similar to that of rubella, was noted in 11 cases. It began on the chest, spread to involve the rest of the trunk, then the arms, and finally the legs, being well marked on hands and feet, particularly the dorsal surfaces. The rash, which sometimes itched, often appeared between the tenth and fourteenth days of illness, lasted three to four days, then faded without staining in the order of appearance. A bright erythematous pruritic rash was seen in two cases, but was thought to be due to penicillin sensitivity.

Periorbital Oedema (Hoagland's Sign).—Periorbital oedema, affecting particularly the upper eyelids, was

present in eight cases. It was more common in the severe anginose form at the height of illness, and lasted two to three days or longer.

Haematological

Atypical mononuclear cells were plentiful in the peripheral blood during the acute phase, often comprising over 80% of the total white cells. This was noted

particularly in the anginose form. Fewer than 10% of atypical cells was not regarded as diagnostic. These cells rapidly disappeared when the temperature settled and the exudate had separated from the tonsils. The lymphocytosis invariably present subsided more gradually. Total white-cell counts of 12,000 to 18,000/c.mm. were common in the well-established case, but within the first few days of the illness leucopenia with

TABLE II.—Summary of Clinical and Laboratory Findings in 80 Cases of Infectious Mononucleosis

Case Number	Age in Years	Sex	Antibiotics given Before Admission	Pathogens in Swabs			Tonsil. Pharyngeal Exudate	Periorbital Oedema	Exanthem	Enanthem	Jaundice	Spleen	Liver		Maximal Reading (Units ml.) Day of Disease in Parentheses		E.C.G. Changes	Maximal Values				Severity of Illness
				Nose	Throat	Post-Nasal							Palpable	Tender	S.G.O.T. (Normal Range 8-28)	S.I.C.D. (Normal Range 2-8)		H.A.T.	W.B.C. per c.mm.	Lymphocytes + Atypical Monocytes %		
1	28	M	Yes	-	-	-	-	-	+	-	-	+	Yes	No	140 (22)	52 (22)	Yes	1:160	14,300	60	Severe	
2	22	F	Yes	-	-	-	-	-	-	-	-	+	No	Yes	80 (9)	24 (20)	No	1:80	7,100	85		
3	19	F	Yes	+	-	-	-	-	-	-	-	+	No	No	26 (9)	13 (21)	No	1:320	18,500	73	Mild	
4	22	F	Yes	-	-	-	-	-	-	-	-	+	No	No	24 (20)	14 (8)	No	1:1,280	16,000	50	"	
5	22	F	Yes	-	-	-	-	-	-	-	-	+	No	No	39 (34)	24 (13)	Yes	1:40	17,700	83	"	
6	35	M	No	-	-	-	-	-	-	-	-	+	Yes	No	28 (23)	14 (23)	No	1:80	9,100	71	Moderate	
7	23	F	No	-	-	-	-	-	-	-	-	+	No	No	120 (22)	24 (29)	No	1:40	11,800	88	Mild	
8	19	F	No	-	-	-	-	-	-	-	-	+	No	Yes	60 (15)	53 (15)	Yes	1:40	9,300	76	"	
9	18	F	No	-	-	-	-	-	-	-	-	+	No	No	140 (12)	32 (12)	No	1:80	16,900	80	Moderate	
10	17	M	No	+	-	-	-	-	-	-	-	+	Yes	Yes	110 (23)	45 (26)	No	1:5,120	9,400	90	"	
11	6	M	No	-	-	-	-	-	-	-	-	+	No	No	28 (27)	17 (41)	No	1:40	12,000	88	Mild	
12	29	M	No	-	-	-	-	-	-	-	-	+	No	Yes	42 (14)	21 (14)	"	1:160	5,300	53	"	
13	21	F	No	-	-	-	-	-	-	-	-	+	No	No	61 (8)	17 (8)	"	1:40	9,000	64	Moderate	
14	24	M	No	+	-	-	-	-	-	-	-	+	Yes	Yes	43 (8)	20 (8)	"	Negative	4,800	76	Mild	
15	19	M	No	-	-	-	-	-	-	-	-	+	Yes	Yes	250 (20)	57 (18)	"	1:320	13,300	85	Moderate	
16	20	M	Yes	-	-	-	-	-	-	-	-	+	No	No	90 (7)	35 (7)	"	1:160	16,900	80	"	
17	20	M	No	-	-	-	-	-	-	-	-	+	No	No	72 (29)	44 (29)	"	1:80	6,300	59	Mild	
18	17	M	Yes	-	-	-	-	-	-	-	-	+	Yes	Yes	42 (14)	18 (14)	"	1:320	11,000	50	Severe	
19	24	M	No	-	-	-	-	-	-	-	-	+	No	No	91 (21)	34 (19)	"	1:160	13,000	83	Mild	
20	9	M	No	-	-	-	-	-	-	-	-	+	Yes	Yes	49 (23)	12 (17)	"	Negative	9,100	76	"	
21	18	M	No	-	-	-	-	-	-	-	-	+	No	No	51 (15)	62 (22)	"	1:640	11,500	70	"	
22	9	F	No	-	-	-	-	-	-	-	-	+	Yes	Yes	410 (2)	60 (2)	"	1:80	4,300	65	"	
23	23	F	Yes	+	-	-	-	-	-	-	-	+	Yes	No	68 (11)	13 (11)	Yes	1:160	7,700	73	Moderate	
24	23	M	Yes	+	-	-	-	-	-	-	-	+	No	No	96 (11)	10 (11)	No	1:80	7,900	85	"	
25	20	M	Yes	+	-	-	-	-	-	-	-	+	Yes	Yes	85 (29)	23 (29)	No	1:640	11,600	90	"	
26	18	F	No	-	-	-	-	-	-	-	-	+	No	No	115 (16)	30 (16)	No	1:640	12,300	90	Mild	
27	20	F	No	-	-	-	-	-	-	-	-	+	No	No	14 (18)	12 (18)	"	1:40	8,100	50	"	
28	14	M	No	-	-	-	-	-	-	-	-	+	Yes	Yes	49 (23)	11 (30)	"	1:320	5,400	68	"	
29	22	M	No	-	-	-	-	-	-	-	-	+	No	No	65 (30)	54 (30)	Yes	1:160	13,100	73	Moderate	
30	20	M	Yes	-	-	-	-	-	-	-	-	+	No	Yes	91 (11)	24 (11)	No	1:1,280	13,500	72	"	
31	20	M	No	-	-	-	-	-	-	-	-	+	Yes	Yes	17 (5)	22 (17)	"	1:160	12,200	75	"	
32	18	F	Yes	-	-	-	-	-	-	-	-	+	No	No	235 (13)	57 (13)	"	1:1,280	15,900	69	"	
33	19	F	No	-	-	-	-	-	-	-	-	+	No	No	60 (23)	26 (23)	"	1:2,560	14,100	82	Mild	
34	18	M	No	-	-	-	-	-	-	-	-	+	Yes	Yes	35 (5)	33 (5)	"	1:160	16,100	84	Moderate	
35	21	M	No	-	-	-	-	-	-	-	-	+	No	No	21 (7)	13 (7)	"	1:5,120	14,000	71	"	
36	11	M	No	-	-	-	-	-	-	-	-	+	No	No	20 (10)	2 (10)	"	1:320	8,100	42	"	
37	20	F	No	-	-	-	-	-	-	-	-	+	No	No	42 (8)	28 (8)	"	1:2,560	13,400	68	"	
38	26	F	No	-	-	-	-	-	-	-	-	+	No	No	32 (25)	33 (12)	"	1:160	6,100	75	Mild	
39	27	F	No	-	-	-	-	-	-	-	-	+	Yes	Yes	108 (9)	32 (9)	"	1:320	13,100	77	Moderate	
40	20	F	Yes	-	-	-	-	-	-	-	-	+	No	No	82 (9)	62 (9)	"	1:5,120	19,900	66	Mild	
41	41	F	No	-	-	-	-	-	-	-	-	+	Yes	Yes	105 (12)	31 (12)	"	1:1,280	13,300	90	Moderate	
42	20	F	Yes	-	-	-	-	-	-	-	-	+	No	No	32 (15)	18 (15)	"	1:1,280	7,900	82	Mild	
43	6	M	No	+	+	+	+	+	+	+	+	+	No	No	37 (15)	12 (15)	Yes	Negative	7,000	84	"	
44	26	M	No	-	-	-	-	-	-	-	-	+	No	No	87 (21)	22 (21)	No	1:1,280	16,000	70	Moderate	
45	21	M	No	-	-	-	-	-	-	-	-	+	No	No	36 (26)	10 (12)	No	1:320	12,300	76	"	
46	25	M	No	-	-	-	-	-	-	-	-	+	No	No	60 (19)	8 (19)	"	1:640	9,900	73	"	
47	14	M	No	-	-	-	-	-	-	-	-	+	No	No	76 (24)	10 (24)	"	1:320	14,600	70	Mild	
48	3	M	Yes	-	-	-	-	-	-	-	-	+	No	No	24 (8)	6 (8)	"	1:80	6,700	87	"	
49	18	F	Yes	-	-	-	-	-	-	-	-	+	No	No	50 (9)	17 (9)	"	1:640	13,900	76	"	
50	28	F	No	-	-	-	-	-	-	-	-	+	Yes	No	75 (15)	21 (15)	"	1:1,280	6,900	62	Moderate	
51	18	F	No	-	-	-	-	-	-	-	-	+	No	No	50 (9)	17 (9)	"	1:640	13,900	76	Mild	
52	18	F	No	-	-	-	-	-	-	-	-	+	No	No	19 (20)	23 (20)	"	1:320	18,100	50	"	
53	19	F	No	-	-	-	-	-	-	-	-	+	No	No	21 (12)	10 (12)	Yes	1:1,280	11,100	64	Severe	
54	22	M	No	-	-	-	-	-	-	-	-	+	No	No	9 (8)	13 (8)	No	1:80	7,700	36	Mild	
55	32	F	Yes	-	-	-	-	-	-	-	-	+	No	No	22 (13)	7 (13)	"	Negative	17,600	56	"	
56	22	M	No	-	-	-	-	-	-	-	-	+	Yes	No	45 (15)	22 (15)	"	1:80	6,800	67	Moderate	
57	19	M	Yes	-	-	-	-	-	-	-	-	+	Yes	No	25 (9)	11 (9)	"	1:5,120	11,000	78	"	
58	20	M	No	-	-	-	-	-	-	-	-	+	No	No	77 (18)	23 (18)	"	1:10,240	8,600	79	"	
59	19	F	No	-	-	-	-	-	-	-	-	+	No	No	47 (20)	17 (7)	"	1:640	23,900	91	"	
60	25	F	No	-	-	-	-	-	-	-	-	+	Yes	Yes	72 (17)	30 (17)	"	1:1,280	18,800	77	"	
61	24	M	No	-	-	-	-	-	-	-	-	+	No	No	31 (12)	10 (12)	"	1:5,120	11,200	68	"	
62	17	M	No	-	-	-	-	-	-	-	-	+	No	No	37 (14)	15 (14)	Yes	1:320	14,200	45	"	
63	3	M	No	-	-	-	-	-	-	-	-	+	No	No	18 (21)	5 (21)	No	Negative	18,800	66	"	
64	19	F	No	-	-	-	-	-	-	-	-	+	No	No	26 (7)	11 (7)	"	1:2,560	12,900	58	"	
65	19	F	Yes	-	-	-	-	-	-	-	-	+	No	No	20 (6)	8 (6)	"	1:640	5,700	43	Mild	
66	21	F	No	-	-	-	-	-	-	-	-	+	No	No	13 (13)	10 (13)	"	1:80	9,200	47	"	
67	15	F	No	+	+	+	+	+	+	+	+	+	Yes	Yes	50 (15)	18 (15)	"	1:160	11,900	68	"	
68	19	F	No	-	-	-	-	-	-	-	-	+	No	No	13 (5)	10 (5)	"	1:40	12,000	70	"	
69	21	M	Yes	-	-	-	-	-	-	-	-	+	No	No	45 (9)	13 (9)	"	1:40	16,000	80	Moderate	
70	20	F	No	-	-	-	-	-	-	-	-	+	No	No	38 (11)	18 (11)	Yes	1:80	13,300	56	"	
71	42	F	No	-	-	-	-	-	-	-	-	+	No	No	36 (19)	20 (19)	No	1:80	9,800	71	Mild	
72	19	F	No	-	-	-	-	-	-	-	-	+	No	No	50 (16)	18 (16)	No	1:80	5,500	46	"	
73	19	F	No	-	-	-	-	-	-	-	-	+	No	No	140 (8)	70 (8)	Yes	1:160	7,500	71	Moderate	
74	19	F	No	-	-	-	-	-	-	-	-	+	No	No	27 (11)	15 (11)	No	1:160	5,900	70	"	
75	18	F	No	-	-	-	-	-	-	-	-	+	Yes	No	23 (5)	27 (5)	"	1:80	8,900	68	"	
76	10	F	No	-	-	-	-	-	-	-	-	+	No	No	35 (15)	9 (15)	Yes	Negative	7,600	81	"	
7																						

a relative lymphocytosis were more usual, at which stage atypical mononuclear cells were often scanty.

Paul-Bunnell Test

A heterophil antibody titre of 1:40 after guinea-pig-kidney absorption was regarded as positive, provided that the titre following ox-cell absorption was 1:10 or less—that is, a difference of two tubes. Heterophil antibody was absent or in low titre during the first week of illness, and reached a maximum during the third and fourth weeks. In one case, however, the Paul-Bunnell test became positive only during the seventh week. In seven cases the Paul-Bunnell test was negative throughout the illness: five of these were children of 10 years or under.

The amount of heterophil antibody in the blood in no way reflected the severity of the disease. For example, Case 18 was very toxic and peritonsillar oedema was so marked as to obstruct respiration, yet the maximal H.A. titre was only 1:320. In several cases where titres of 1:5,120 or higher were recorded the disease was considered to be moderate or mild (Table II). Nor was there correlation between the degree of enzyme activity and the H.A. titre. In Case 22 the maximal H.A. titre was only 1:80, yet the serum glutamic oxaloacetic transaminase (S.G.O.T.) reached a level of 410 units/ml. and the serum isocitric dehydrogenase (S.I.C.D.) 60 units/ml.

Complications

It is now recognized that infectious mononucleosis carries the risk of a formidable variety of complications affecting practically every tissue and organ in the body. It is of paramount importance that this fact should be appreciated, as the view held in some quarters that it is a trivial disease is to be deprecated. In my experience the majority of patients complained of lassitude, anorexia, inability to concentrate, and other manifestations of general systemic upset for many weeks and even months after the acute phase of the disease had subsided.

Hepatitis

One of the facts which have emerged from this work is that hepatitis occurs in practically every case and probably should now be regarded not so much as a complication as part of the syndrome of infectious mononucleosis.

Repeated conventional liver-function tests and enzymological estimations—S.G.O.T. and S.I.C.D.—were done in every case and liver biopsy in one instance. The findings have been analysed in detail and will be the subject of another paper. Here some clinical implications of these tests are briefly considered. The following biochemical methods were employed (normal ranges are indicated within parentheses): S.G.O.T. (8–28 units/ml.), Reitman and Frankel (1957); S.I.C.D. (8/28 units/ml.), Bell and Baron (1960); serum proteins (6–8 g./100 ml.), Wolfson *et al.* (1948); serum bilirubin (0.1–0.8 mg./100 ml.), Reiner (1953); alkaline phosphatase (3–13 K.-A. units), King and Armstrong (1934); thymol turbidity (0–4 units) and thymol flocculation (0–1 plus signs), MacLagan (1944); colloidal gold flocculation 0–1 unit, MacLagan (1944); and zinc sulphate turbidity (0–8 units), Kunkel (1947).

Conventional liver-function tests often failed to reflect minor changes in the liver and were frequently normal in the presence of greatly increased enzyme activity. The serum bilirubin was raised in 26 (33%) cases. Jaundice

was present in 12 (15%) cases, and the liver was enlarged or tender in 27 (34%) cases. The S.G.O.T. was raised in 58 (73%) and the S.I.C.D. in 74 (93%) cases.

The degree of hepatocellular damage was unrelated to the severity of infection—for example, in Case 22 the disease was considered to be mild, yet enzyme activity was relatively high (S.G.O.T. 410 and S.I.C.D. 60 units/ml.). There was frequently wide daily fluctuation in enzyme activity, but generally titres were maximal between the second and fourth weeks and had mostly returned to normal by the end of the sixth week. Case 19 provides an excellent example of the mild anginose form.

A woman aged 24 complained of nausea and loss of appetite 13 days before admission. She was pyrexial and was given oral penicillin by her doctor. Ten days later she developed sore throat and enlarged cervical and suboccipital

FIG. 2.—Typical findings in a case of mild anginose infectious mononucleosis.

glands. The temperature was then 102° F. (38.9° C.). A rash appeared on the trunk the day before admission. On examination there was a fine dusky macular rash on the trunk and limbs. Creamy, easily removable exudate covered both tonsils. Cervical, suboccipital, and axillary glands were enlarged. The spleen was not palpable and the liver was neither enlarged nor tender. Heart, lungs, and central nervous system were normal. B.P. was 130/80. Schick and Dick tests were negative and chest x-ray examination showed nothing abnormal. The rash faded and the tonsils were free from exudate on the fourth day after admission. The patient was discharged after 19 days in hospital.

TABLE III.—Six Cases of Infectious Mononucleosis with Normal S.I.C.D. Tests

Case No.	Age in Years	Sex	Day of Disease	Severity	T/P Exudate	P-B Test	Units/ml.	
							S.I.C.D.	S.G.O.T.
36	11	F	10	Moderate	+	1:320	2	20
46	25	M	19	Moderate	+	1:640	8	60
48	3	M	8	Mild	+	1:80	6	24
55	32	M	13	Moderate	+	Neg.	7	22
23	3	M	21	Moderate	+	1:2,560	5	18
65	19	F	<6	"	+	"	8	20
			<14	"	+	"	7	10

Of six cases with normal S.I.C.D. values, five for various reasons had enzyme estimations done on only one occasion (Table III). There was no clinical evidence of hepatitis in these cases. Standard liver-function tests were virtually normal although in Case 36 alkaline phosphatase was 24 units, and in Case 46 the thymol turbidity was 5 units. In view of the wide daily variation that may occur in enzyme activity an isolated normal reading does not entitle one to assume that the liver is undamaged.

Myocarditis.—Electrocardiographic changes, usually indicating non-specific myocarditis, were seen in 13 (16%) cases. An abnormal T wave was the commonest single finding, but in Case 24 there was evidence of partial right bundle-branch block, and in Case 29 of pericarditis (Figs. 3 and 4).

FIG. 3.—Case 24. E.C.G. showing slurred S in lead I and notched R in lead III. There is an RSR' complex in V_4R and V_1 where $R=S$. This record is compatible with partial right bundle-branch block.

FIG. 4.—Case 29. E.C.G. showing low-voltage T throughout. T is diphasic in leads II, aV_1 , and leads V_4-V_6 . T is inverted in aVF . There is a deep S in V_1 . Repeat E.C.G. six days later showed ST elevation in leads II, V_4-V_6 . T was no longer inverted. These records were compatible with a diagnosis of pericarditis.

FIG. 4

Other Complications.—One patient developed right-lower-motor-neurone facial paralysis. There was occasional radiological evidence of enlarged hilar glands, but otherwise no pulmonary lesions were seen. Renal and haematological complications were not encountered.

Treatment

The possibility of myocardial involvement and the almost invariable occurrence of hepatitis made complete bed rest during the acute phase of the illness advisable. Convalescence was gradual and the patient was discharged only when the E.C.G. returned to normal and the enzyme activity to normal or near normal. The average length of stay in hospital was three weeks. Complaints of irritability, fatigue, and inability to concentrate were common many weeks, and even months, after discharge from hospital. One patient complained of lack of libido for several months.

Antibiotics.—Chemotherapeutic agents and antibiotics had no effect on the course of the illness, although secondary throat infection logically demanded appropriate chemotherapy.

Steroids.—In anginose forms with extensive faucial inflammation and oedema rapid relief was obtained with

steroids. Prednisolone was commonly employed, adult dosage being 45 mg. on the first day, reduced by 10 mg. daily, and discontinued after five days. Antibiotic cover was always given to patients on steroid therapy.

Discussion

In view of the protean nature of the disease diagnosis is by no means easy. The anginose form may readily be mistaken for acute tonsillitis, in which event the patient is commonly referred to hospital as a case of "tonsillitis which has failed to respond to antibiotics." Alternatively, the condition may, understandably, be mistaken for diphtheria. Thick exudate spreading outside the territory of the tonsils, plum-coloured injection of the fauces, peritonsillar oedema, cervical lymphadenitis, often with periadenitis, may be almost identical in the two conditions. The history of malaise, headache, anorexia, and lassitude for a few days before the onset of sore throat points to infectious mononucleosis, and the enanthem, when present, strongly supports this diagnosis. Fortunately, at this stage in infectious mononucleosis the white-cell count is almost invariably typical, and should be done as a matter of urgency.

During the first two or three days of the illness, when the only clinical findings are, as a rule, pyrexia and lymphadenopathy, there is often a leucopenia with distribution characteristic of other virus infections. The Paul-Bunnell test at this stage is often negative, but by the end of the first week atypical mononuclear cells are present in significant numbers in the peripheral blood.

Although palatal petechiae have been noted in rubella (Forchheimer, 1898), in herpangina (Huebner *et al.*, 1951), and in pharyngo-conjunctival fever (Kendall *et al.*, 1957), they occur much more commonly in infectious mononucleosis, and, when seen, constitute a valuable diagnostic aid. Caird and Holt (1958) described four different varieties of enanthemata—petechiae, linear pink macules, red circular macules, and white macules. In this series petechiae and red macules were seen most frequently, usually at the junction between the soft and hard palates. It is imperative that the mouth be examined daily as these lesions not infrequently fade within 24 hours.

A variety of rashes—vesicular, herpetiform, scarlatini-form, maculopapular—have been noted (Stevens, 1952). In this series the rash, apart from that thought to be due to penicillin sensitivity, was rubelliform in character and was concentrated most profusely on the trunk and the proximal parts of the limbs. It often occurred early in the illness, and in one case was the presenting symptom along with posterior cervical lymphadenopathy. In this instance the provisional diagnosis of rubella could not be challenged until the white-cell count, and subsequently the Paul-Bunnell test, showed conclusively that the condition was in fact infectious mononucleosis.

The liver in infectious mononucleosis has been investigated by conventional liver-function tests (Leibowitz, 1953), biopsy (Nelson and Darragh, 1956; Sullivan *et al.*, 1957), and transaminase estimation (Rennie and Wroblewski, 1957; Rosalki *et al.*, 1960). Rosalki pointed out that conventional liver-function tests are insensitive indicators of liver damage and are unreliable when the presence of antibodies in the serum may affect flocculation. Both liver biopsy and transaminase estimation suggest that hepatitis is present in as many as 80%

of cases. Findings in this series support the value of transaminase estimations, but suggest that S.I.C.D. activity is an even more delicate measure of hepatocellular damage. Enzyme tests showed that activity was maximal during the second to fourth weeks of the disease, some time after the pyrexia and angina of the acute phase had subsided. This interval is compatible with an allergic reaction to infection. In the great majority of cases the enzyme tests had returned to normal by the end of the sixth week.

S.I.C.D. has been found to be raised in hepatocellular damage but normal in a wide variety of conditions involving tissue damage in other organs—for example, in myocardial infarction, malignant diseases not involving the liver, collagen diseases, and numerous infective states (Sterkel *et al.*, 1958). In this department it was also found to be normal in virus infections such as measles, mumps, rubella, and chicken-pox. The test is therefore both a sensitive and a specific guide to hepatocellular activity, and, because it is almost invariably positive in infectious mononucleosis, may at the same time provide a useful diagnostic aid.

Hepatitis can be adequately assessed by twice-weekly enzyme estimations. In view of the superiority of the S.I.C.D. test this alone provides the essential information. No patient should be discharged from hospital until the S.I.C.D. is normal or near normal.

In a report on 223 cases Wechsler *et al.* (1946) found significant changes in the electrocardiogram in 53 (23%). Abnormal T waves were most frequently encountered, but in two patients there was temporary heart-block. Transitory bundle-branch block (Smith, 1957) and pericarditis (Webster, 1957) have been described. Analysis of electrocardiograms in this series confirm that altered T waves are the commonest single abnormal finding, although the possibility of more serious conditions such as bundle-branch block and pericarditis have to be considered. As with enzyme estimations, twice-weekly E.C.G. recordings are desirable and the patient should be kept at rest until there is no longer evidence of active myocarditis.

Neurological complications were encountered in only one case. Pulmonary lesions, so often described (Wechsler *et al.*, 1946; Vander, 1954; Briggs *et al.*, 1956), were not seen despite routine radiological examination in every case.

Finally, it is imperative to stress the need for prolonged convalescence if the patient is to be spared a sense of frustration and lack of confidence that inevitably supervenes when he finds he is unable to carry out his normal activities

Summary

Eighty cases of infectious mononucleosis admitted to the Royal Free Hospital, London, over a period of three years have been studied: 59 (74%) were in the age-group 15–25 years, and 43 (73%) of these were females. The anginose form predominated, particularly in this age-group. Conventional liver-function tests, enzymological estimations, electrocardiograms, and chest x-ray examinations were done in every case.

Hepatitis occurred so often, as shown by enzyme tests, that it is perhaps justifiable to regard it as part of the syndrome of infectious mononucleosis. Serum isocitric dehydrogenase activity was the most sensitive and specific indicator of hepatocellular damage, and was increased in 74 (93%) cases. It was maximal during

the second to fourth weeks and usually returned to normal by the end of the sixth week. It also provided a useful guide to clinical progress, and for this purpose should be repeated twice weekly.

Myocarditis was present in 13 (16%) cases, and, in conjunction with hepatitis, probably accounted for the weariness and mental apathy which so frequently persisted for weeks and even months after the acute infection had subsided.

Antibiotics were of no value unless there was secondary throat infection, but the dramatic effect of steroids in the anginose form is stressed.

Diagnostic problems are discussed and it is suggested that clinical, haematological, and serological considerations should be taken into account in arriving at a final diagnosis. The characteristic enanthem seen in 33 (41%) cases was a particularly helpful diagnostic feature.

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