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INFECTIOUS MONONUCLEOSIS IN JAPAN*

With Special Reference to Classifying into Sporadic Infectious Mononucleosis and Epidemic Glandular Fever.

Toshio OGINO, M. D.*

A disease supposed to be infectious mononucleosis was first described by Filatov,²⁰⁾ a Russian pediatricist, and claimed, in 1889, to be a clinical entity by Pfeiffer⁶⁷⁾ of Germany and was named "Drüsenfieber." The history of its study since then is divided into four periods by Houck³¹⁾; clinical description 1885-1920, hematologic period 1920-1932, serologic period 1932-1944 and pathologic description 1944 to date. Ozawa⁶⁴⁾ of Japan, independently of Pfeiffer, described a disease so-called Tokushima-Fever in 1891, and 1924 Ohtawara et al.⁶¹⁾ insisted that there was no difference between the disease called "Kagami-Fever" in Kyushu and the infectious mononucleosis in Europe and America and advocated that Kagami-Fever should be called "epidemic glandular fever (Ryukosei Sennetsu in Japanese)." Later, Ohtawara et al.⁶³⁾ and others³²⁾³⁸⁾⁷¹⁾ perceived that Kagami-Fever, Hyuga-Fever, Tosa-Fever and Tokushima-Fever which have been found in various areas of Kyushu and Shikoku districts were the same disease as the infectious mononucleosis. In 1954, Misao and Kobayashi⁵⁰⁾⁵¹⁾ claimed that they were able to isolate the etiological agent of Kagami-Fever and named it "Rickettsia sennetsu Misao et Kobayashi."⁵³⁾ Thus, the studies on this disease have developed successfully in Europe and America as well as in Japan. However, there has recently been a tendency, that the study of this disease is going back again to the situation of the early period, that is, the second period named by Houck. This implies a question, is this clinical entity a highly contagious as influenza or a sporadic type of less contagious nature? Tidy and Daniel⁸⁰⁾ (1923) stated, "Glandular fever and the condition described as infective mononucleosis are identical," but Downey and McKinlay¹³⁾ (1923) described, "From glandular fever, with its highly epidemic nature, its occurrence in children, and its absence of tonsillitis or marked pharyngitis, differentiation is also clear." Evans and Robinton¹⁸⁾ (1950) presented the question, through their etiological studies,¹⁵⁾¹⁶⁾ a reason why epidemic of the infectious Mononucleosis had diminished; and Shubert et al.⁷⁴⁾ (1954) advocated that the disease should be divided into two types, namely, epidemic and

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*Preliminary accounts for parts of this paper were read at General Meetings of the Hyogo Medical Association in 1953 and 1954, and at 57th and 58th General Meetings of Japanese Pediatrics Society in 1954, 1955.

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sporadic. The conditions of Kagami-Fever as studied by Ohtawara and Misao are endemic, sporadic and low contagion. This fact had been proved through the discovery of an etiological agent by Misao. Detailed descriptions that paid an attention to an epidemic occurrence in Japan of this disease were reported in 1954 by C. Oguro and S. Oguro⁵⁸⁾ (with Torikai,⁸¹⁾ read at the 42nd Niigata Medical Meeting, 1949), Ohshiro et al.⁶⁰⁾, as well as by the present author.⁵⁵⁾⁵⁶⁾⁵⁷⁾ It appears, therefore, that the study on infectious mononucleosis has reached again a stage where further analysis from clinical and epidemiological points of view are in order. Present paper is a report of the author on an epidemic of infectious mononucleosis which broke out in 1953 at Wada-Mura, Hikami-Gun, Hyogo-Prefecture. The disease was first found among primary school children and then spread in the whole population of the village, and recurred in the following year. Present study emphasizes an interpretation on the differences between sporadic and epidemic character of the disease as compared with the related cases found in Europe and America as well as in Japan.

I. Epidemic Occurrence of 1953

1. Epidemiology

A disease broke out rather abruptly on and about May 15th, 1953, among higher grade pupils in a primary school of Wada-Mura, Hikami-Gun, Hyogo-Prefecture, Japan, which soon prevailed in the whole population of the village.

The patient, supposed to be the first case, had been absent from the school from 13th of May. School class "5 A" ("A" group of the 5th grade), to which the first patient belonged, had 16 absentees (this was the highest number) among 51 pupils on May 18th. The total number of pupils absent from school in the 5 A class during May was 37. (In this school there was, at that time, no prevalence of any disease except for measles; and almost all pupils of the 5th and 6th grades suffered previously from measles.) Then the disease spread to other grades, both higher and lower, and from the pupils to their families. It was not rare at that time to see all persons in one family to be confined. The author stated in his previous report,⁶⁰⁾ "The majority of 6516 persons living in this village have been supposedly infected clinically or subclinically if they were examined carefully." And Masuda⁴⁰⁾ had undertaken his investigations when a similar outbreak recurred one year later at Nakatakeno-Mura, and described that 61.3% of all the families were infected. (Fig. 1 and 2) The clinical cases were found evenly irrespective of age and sex; but when healthy adults were affected, usually they did not take to their beds. Generally speaking, younger people, 15 to 25-year-old, seemed to have shown most serious symptoms, particularly when they were forced to rest in bed. As with adult cases, few of the patients, especially lower grade pupils and infants, who had not yet been infected with measles, came to the author's consultation, because they usually were free from fever while they were attended at homes, being thought to have caught

measles. But it was found that almost all people belonging to the families of the patients being attended by the present author, had been infected with this particular disease or were in the situation that they would be infected within about a fortnight. The number of patients actually examined and diagnosed as suffering purely from this disease only, were 50 cases on the 20th of June. Their age ranging from 0 year to 5-year-old, 4 persons; from 6 to 15, 29; 16 to 25, 8; 26 to 50, 2; over 50 years, 7; male 22; female 28. The monthly incidences are as follows: May, 31; June, 25; July, 11; August, 2; September, 11; October, 1; November, 0; December, 8—total 89, but 39 cases, from 21st of June to December, are not covered by this report, as the essential facts and conclusions would not be altered by including the latter cases. Cases which occurred in 1954 will be stated in Part II, as they were not diagnosed by the author till May. The epidemics occurred mostly in Spring, ⁶⁾⁴⁶⁾⁵⁸⁾⁵⁹⁾⁶⁰⁾⁸⁰⁾⁸⁵⁾⁸⁸⁾ but some cases were observed in other seasons: Winter, ⁸⁾²⁶⁾⁸⁴⁾ Summer, ²⁷⁾⁵⁸⁾⁸¹⁾⁸⁶⁾ and Autumn. ¹²⁾²³⁾⁵⁴⁾⁶⁶⁾⁷⁴⁾⁷⁸⁾

The progress of infection was much like influenza as mentioned before. At school no meals were provided for the pupils; nobody traveled on whole school excursions or in groups since May, and no class pupils in which the first patient appeared took specific foods and drinks in the same manner. It is the author's belief, that a mode of infection of the present disease may be droplet infection, for most cases accompanied a symptom of cough.

An incubation period seemed to be about 5 days. Two boys, 5 and 7-year-old, who came from non-prevalent part (Takamatsu) suffered from the disease 5 days after their arrival at Wada-Mura. The younger became feverish, the older passed to an

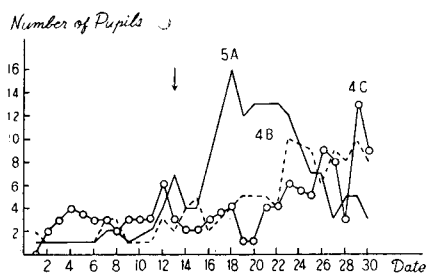


Fig. 1 Showing number of absentees in each grade during May, 1953. 5A, 4B, and 4C indicate grades and classes (5th and 4th grades; classes A, B and C). Other grade are omitted. The presumptive first patient was in 5A class.

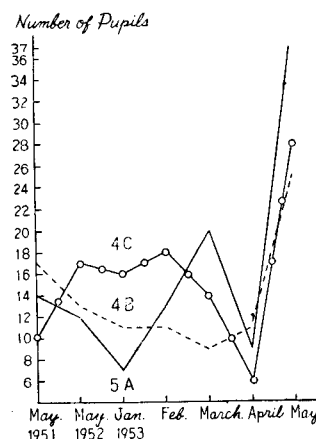


Fig. 2. Showing number of absentees during May, 1951, 1952, and during each month, 1953. (Not showing the total number of days of absentees.) The grouping of pupils in each grade of each year is unavoidably different from that of the previous year. The presumptive first patient was in 5A class.

afebrile condition. Presumed incubation period varies in each reported epidemic: 1 day,⁸⁾ 2 days,⁷⁾ 5-6 days,²⁷⁾⁵⁹⁾ 7-9 days,²³⁾⁸⁰⁾⁸⁸⁾ 1-9 days,⁸⁰⁾ 10-12 days,⁸⁰⁾ 10-14 days.¹²⁾ The description by Halcrow et al.²⁷⁾ is noticeable. He reported, "The incubation period in our cases varied from 5 to 10 days: in one instance, it was exactly 5 days."

2. Clinical Findings

(1) *Diagnosis*: The author suspected the present disease when the following symptoms were observed: marked papillary proliferation of the tongue (many of those may be called mild strawberry tongue), and swelling of submaxillary (including submental) and of cervical lymphatic glands. These two major symptoms could be noticed almost in every case. Tonsillitis, stomatitis, tubercular lymphadenitis and others were excluded clinically.

(2) *Prodromic symptoms*: General languor, anorexia could be noticed from 2 to 5 days prior to temperature-rise in almost all cases.

(3) *Chief complaints*: Fever feeling, 46% out of 50 persons (case number and percentage are always based on 50 cases unless otherwise indicated), general languor 18% (this number represents the cases in which this symptom was recorded as the major complaint; general languor itself was found in all cases), abdominal pain 12%, sore throat 8%, cough 6%, headache 4%, vomiting 2%, pain in the chest 2%, epistaxis 2%.

(4) *Mode of occurrence*: Patients with pyrexia became feverish rather suddenly with chills. Some of the patients could not be sure at what date they fell ill. In such cases the author presumed the first onset uniformly to be the date when they began feeling unusual. Wechsler et al.,⁸⁰⁾ also, stated, "It is very difficult to arrive at any satisfactory conclusion concerning the duration of the attack."

(5) *Temperature*: The highest temperature at time of the first consultation was 39.4°C. The highest recorded during the course of the disease was 40.2°C, but usually from 38.0°C to 39.0°C. In high temperature type, it was common that pupils about 10-year-old had temperature of about 38.0°C for one day (rarely two days), which fell down on the following day, and did not rise again. Patients, 16 to 25-year-old, after having high temperature for two or three days, had ordinary temperature for one or two days and again became feverish for about one day. Thus many cases showed a saddle-backed type fever with duration of about one week. In low fever type, temperature-rise of 37.1°C to 37.5°C continued for about two weeks. In apyretic type, most adults showed no fever. They passed lazily two or three days complaining of general lassitude and stiff shoulder. Children showed usually the same fever type as school pupils about 10-year-old. At time of the first consultation, patients with temperature below 37.0°C, 26%; those with temperature of 37.1°C to 37.5°C, 26%; these figures show that about half of the cases consulted were of febricula or apyretic. (Fig. 3) Wechsler et al.⁸⁰⁾ described, "There were 377 cases

among 556, who exhibited an elevated temperature. The elevation lasted for only one day in 97 of these cases. One week or less, 89%. There were 18 cases who exhibited a low-grade fever for a period varying between two weeks and three months." This observation is similar to what has been observed here in Japan by the authors. The resemblance of these two observations made independently under different conditions, and their marked difference from what have been observed with sporadic cases are of interest. Pfeiffer,⁶⁷⁾ who gave the name of "glandular fever," stated two types in which the durations of fever were 1-2 days and the saddle-backed type lasting for 8-10 days.

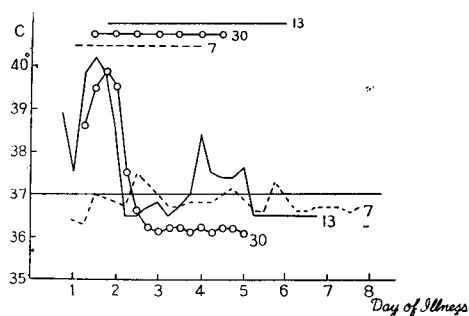


Fig. 3. Showing fever types, (each number shows number of patients); No. 7 represents a low fever type and No. 13 represents a saddle-backed type. (Each exists in Table 1 and Table 2.) No. 30 represents a type generally found in the majority of the pupils. All of these are representative cases observed since the early period of the illness. Three horizontal lines shown in the upper part indicate periods, during which sulfathiazole was administered.

(6) *Pulse*: In the cases of adult patients bradycardia was often observed, and at high temperature period no pause was seen in an case. Bernstein⁶⁾ and McKinlay⁴⁷⁾ have reported bradycardia in sporadic cases.

(7) *General appearance*: These patients with facial congestion and high fever of about 38.5°C still sometimes looked cheerful, and some of them even attended school. In adults, they complained little and during a period of pyrexia, they felt lassitude but could be out of beds, which is entirely different from influenza.

(8) *Naso-pharyngo-glossal symptoms*: About half the patients discharged sero-mucoid secretion from nose at an early period; sneezing was complained, but limited to a few cases. Many complained of coughing as the main symptom which continued persistently. Those who had no cough, began to complain after fever fell. No phlegm noticed, irritating cough was complained by 60 percent at the time of first attendance. 52 percent had sore throat; itchy feeling in the throat; painful when coughing, but no pain while swallowing foods. Some said they felt something like an insect coming up in the throat. There are characteristic complaints which differed plainly from complaints in the case of tonsillitis. Patients who had pain while swallowing were only two. As stated previously, tonsillitis was excluded when it was observed clearly at the first consultation. Of course, in some case of children there existed tonsillar hypertrophy or slight pharyngitis when they coughed. In the middle period of prevalence, one adult case of peritonsillar abscess, and one case of tonsillitis with aphthous stomatitis and gingival bleeding were noticed. Both were accompanied with submaxillary lymphadenoma, marked papillary proliferation of the tongue.

But as it was not clear whether these cases should be classified under the present disease or not, they were excluded from the number of 50 patients. The marked papillary proliferation of the tongue was noticed in all cases. There were only three cases without the sign of tongue at first attendance but it became pronounced by the second consultation. Generally the symptom was most distinct about one week after onset of the disease. In many cases it presented a picture of mild strawberry tongue. Even on 45th day proliferation and reddish change of papillae of entire tongue were noticed in many cases. The papillary change appeared in an early period on the tip of tongue, then on edge, and on central part swollen appearance of colorless papillae fungiformes was noticed. Although no description on this sign has yet been found in the literatures, this was very conspicuous in the Hyogo epidemics. Some had greyish fur. With aged patients, or patients in bed with other diseases, there were signs of peculiar reddish, purple color, like beef appearance of the tongue which was flat and eroded, but wholly incrassated, with increase of sulcus linguae, and complained of total lack of appetite. Koplic's spots were not noticed in all cases. However, in June, 1954, Palatal Enanthem (Bender)⁹⁾ was noticed in an infant on the second day of illness, its clinical value was uncertain as it was only a single case experienced.

(9) *Eye symptoms*: There were hardly no signs of conjunctival congestion. No bleeding was found in any case.

(10) *Lymphadenoma*: Swelling of submaxillary glands appeared in all cases. The largest was found a size of a thumb tip in one adult case. Others were of a forefinger tip size or smaller, but mostly of a size of little finger tip or of a soya bean. Tenderness could not be elicited, only one patient was conscious of swollen glands, these were of somewhat hard consistency, but felt less hard in older patients. Cervical glands swollen earlier in some cases, but after about a week, they were definitely swollen, and in one case particular enlargement became as large as a size of sparrow's egg. In most instance, the swelling of submaxillary and cervical glands was shown persisting more than 45 days. Nape of the neck, retroauricular, occipital glands were not swollen. Swelling of axillary, femoral, inguinal glands totaled 64 percent, which became size of a little finger tip to a red bean without tenderness. The swelling of submaxillary glands was of particular importance, besides tongue signs as mentioned previously. It was true that, based on this observation, the author considered this disease as a peculiar epidemical infection. In the author's opinion, these were the features which occurred among Japanese people in a virgin soil for this disease. It should be noted here the report of Feer¹⁰⁾ that "Simultaneously with or $\frac{1}{2}$ - 1 week after a fever, marked swelling of nape of the neck and especially of the submaxillary glands was brought about."

(11) *Nervous symptoms*: 52 percent of them complained of headache at the initial onset. Arthralgy, lumbago were complained of only when healthy adults were confined with fever, but not as much as influenza. Of fifty cases seen in 1953, none showed symptoms similar to encephalitis or cerebrospinal meningitis, although, in

1954, the author found two adult cases with severe protracted headache presenting a picture of cerebrospinal meningitis. Following the subsidence of fever 8 percent developed of rheumatic pain of the lower extremities, there were also 8 percent who had chest pain on breathing.

(12) *Respiratory symptoms*: Those who had bronchitis confirmed by auscultation numbered 14 percent but they were negative on percussion.

(13) *Abdominal symptoms*: Many of the patients complained of abdominal pain (26% at first attendance). When patients complained of abdominal pain as a main symptom, such pain continued stubbornly for about a week. There was no tenderness elicited such as seen in the case of appendicitis. 14 percent had vomiting and 26 percent of the patients had palpable liver, the largest was two fingers' breadth. Some felt tenderness with respiratory movements. No jaundice was seen but in one case the spleen was felt. One case had diarrhea, but others had either constipation or regular movements. Anorexia was a common symptom.

(14) *Circulatory symptoms*: Nothing special to be mentioned.

(15) *Hemorrhagic manifestations*: 12% had epistaxis at first consultation. Generally hemorrhage appeared at an early period. Uterine hemorrhage, 1 case; purpura on lower limbs, 1 case. Rumpel-Leede's phenomenon was tried on several patients, but was always negative.

(16) *Eruption*: 32% had rash. Three kinds of rash appeared: (i) resembling goose skin, (ii) resembling rose-spots, and (iii) hemorrhagic type. (i) Rash resembling goose skin showed papular elevation from skin, colourless, 2-3 mm in diameter, a little larger than usual goose-skin, found in groups in the epigastrium, ventro-dorso-thorax and on the shoulder. The tip was somewhat lustrous. (ii) Rose-spots like rash was 3-4 mm in diameter, pink, raised a little, distributed whole body but disappear on pressure. They do not coalesce. (iii) Hemorrhagic eruptions having petechiae in center, were macular and surrounded by round red halo of 3-7 mm in diameter, which disappear on pressure. Twelve or thirteen of these erupted at one time on the waist line, disappearing less than 24 hours but the central petechiae remained. The other types of rashes also seemed to fade quickly. The occurrence was in all cases in early period. Pruritus did not accompany. Eruptions could be well differentiated from German measles, measles, scarlet fever, or Izumi fever. There have been many reports on epidemic of this disease, in which rose-spots like rash²⁷⁾⁷⁹⁾⁸⁶⁾ and hemorrhagic rash²⁷⁾⁸⁶⁾ resembling those observed by the present author are described. Sweating was a common symptom.

3. Laboratory Findings

(1) *Urin*: Among 27 cases examined, including examination after the first consultation, urobilinogen positive, 21 cases, protein positive, 5 cases. Diazo-reaction, bilirubin were all negative. Urobilinogen was still positive in some cases even 21 days after the onset of their illness.

(2) *Blood*: As shown in table 1, among 9 cases tested, acceleration of erythrocyte sedimentation rate, 4 cases; increase of total white cells at first attendance, 5 cases. In differential white cell counting, many cases showed eosinophilia. The fact that there were two cases (No. 7 and No. 13) showing decrease of the eosinophils during the convalescence, suggests that it was not due to helminthic infection. There have been many literatures, in which eosinophilia during the convalescence was demonstrated both in epidemic and sporadic cases of this disease.⁽²⁴⁾⁽²⁷⁾⁽³⁷⁾⁽³⁸⁾⁽⁴³⁾⁽⁶⁶⁾⁽⁶⁶⁾ Particularly, descriptions on the eosinophilia during the acute phases by Glanzmann,²⁴⁾ Kaufman³⁷⁾ and C. Oguro and S. Oguro⁵⁸⁾ appear to be interesting. There were many cases of monocytosis. In an early period a left shift of the nuclear number of neutrophils was noticeable. The degree of lymphocytosis and relative increase of mononuclear cells (including lymphocytes, monocytes and plasma cells), to be called mononucleosis, is low. "Downey (I)" in Table 1 means round or oval large cell, its long diameter being 1.5 to 4 times, and its short diameter 1.5 times as long as those of red cells, respectively. Such cells contained a larger amount of cytoplasm which stained perbasophilic and often included vacuoles. Its nucleus was round, oval or kidney-shaped

TABLE 1. Blood Findings in 1953

Case No.	Age	Sex	Day of Illness	Erythrocyte Sedimentation Rate (average of 1h. & 2h.)	White Blood Cells	Eosinophils %	Basophils %	Neutrophils %			Lymphocytes %				Monocytes %	Plasma cells %	Mononucleosis %	Note
								Stab.	Seg.	Total	Large	Small	Downey (I)	Total				
7	11	M	1	8	15,400	28	0	11	31	42	2	24	0	26	4	0	30	
			8		17,100	18	0	8	31	39	7	28	4	39	4	0	43	
8	11	M	3	24	12,200	1	0	32	42	74	0	12	1	13	12	0	15	
			10		8,500	13	1	3	42	45	5	32	1	38	3	0	41	
11	8	F	3	9	6,100	0	0	16	38	54	4	24	1	29	17	0	46	serious
			9		11,800	17	0	4	39	43	1	37	0	39	2	0	41	
13	17	M	2			0	0	22	52	74	5	5	1	11	15	0	26	serious
			7			2	1	5	17	22	22	42	8	72	3	0	75	
18	11	F	5	30	10,400	8	0	9	23	32	11	39	3	53	7	0	60	
			9			3	0	15	40	55	8	31	0	39	3	0	42	
19	9	F	2	48	19,300	8	0	30	40	70	5	10	1	16	6	0	22	
			5			32	0	3	7	10	31	20	6	57	1	0	58	
12	10	F	1	7	8,500	0	0	26	48	74	1	14	0	15	11	0	26	slight
23	17	F	2			5	0	4	57	61	11	21	0	32	2	0	34	
25	18	M	3	3	5,600	0	1	36	32	68	8	15	0	23	8	0	31	serious
26	8	F	4	24	5,900	0	0	27	21	48	4	38	0	42	10	0	52	
29	9	F	5	7	12,600	4	0	35	25	60	8	21	0	29	7	0	36	
5	12	M	31	2*		36	1	5	10	15	14	17	1	32	16	0	48	
44	6	F	13			3	0	20	34	54	6	34	0	40	3	0	43	case of relapse *after relapse

etc, lighter and more coarse, when dyed, than nucleus of lymphocyte, and contained chromatin gross masses. Generally, cytoplasm stained deep; in some of the cells, however, the cytoplasm exhibited a semi-circular part which stained lighter particularly in the area coming in contact with the nucleus. When compared with many descriptions by other investigators, as well as coloured atlas in text books,⁶⁾¹⁷⁾¹⁸⁾²¹⁾²³⁾²⁴⁾²⁵⁾²⁷⁾²⁸⁾⁴¹⁾⁴⁶⁾⁷⁶⁾⁸⁰⁾⁸⁹⁾ they appeared identical with Downey's I type cells¹³⁾ and so-called "Virocyte" by Litwins and Leibowitz⁴⁰⁾ who extended the meaning of its appearance to other viral diseases. No case of II and III types (in Downey's description) were found. Izumi³⁴⁾ stated in detail that this cell was quite different morphologically from Turk's type of the plasma cell. Amano¹⁾ stated that he supposed it identical with his "Lymphogonia."²²⁾ Although many lymphocytes had features which come close to Downey Cells because of a few vacuoles as well as their a little weaker basophilic nature, they were differentiated by the present author from Downey Cells for the difference of sizes and stainability. Unno and Hanaoka⁸³⁾ reported interesting experiments, in which the transition from lymphogonia to large lymphocyte even in blood was demonstrated. No lymphoblast was found by the present author.

(3) *Serologic tests* (See, Table 2.):

Widal test: With *S. paratyphi A*, one case 1: 640, others below 1: 160.

Weil-Felix reaction: With *Proteus OX19* one case 1: 160, others below 1: 80.

Influenzal hemagglutination test: (Tested according to the "Guides for Examination"⁸⁷⁾ issued by the Welfare Ministry of Japan.) Many cases showed high titers for type A'. Two cases showing titers of 1: 16, 1: 4, respectively, were found; others were below 1: 2. This village had experienced influenza during February and March of 1953, but serological type of the etiologic virus was not confirmed. It should be noted, however, that in another place of Hyogo-Prefecture, A' type of virus was isolated during that epidemic.

Paul-Bunnell reaction: (This was performed by the method established by the Research Committee on Infectious Mononucleosis of Japan.) Details of the techniques were as follows; Defibrinated sheep erythrocytes were washed three times with physiological saline by centrifugation at 3000 r.p.m. for ten minutes. The packed erythrocytes were resuspended into 0.5% suspension with physiological saline containing one tenth volume of M/15 phosphate buffer (pH. 7.4). Serum, inactivated by heating at 56°C for 30 minutes, was diluted with buffered saline by two-fold dilution (from 1: 5 to 1: 5120). 0.25 ml of diluted serum was added with 0.1 ml of 0.5% sheep erythrocytes and the mixture, after shaking thoroughly, was incubated at 37°C for one hour and then kept at 4-10°C for twenty hours. Final dilutions of serum were from 1: 7 to 1: 7168.

Controls consisted of serums from three healthy adults, titers of which were 1: 56, 1: 28, 1: 14. Titers more than 1: 224 even at one time were 9 cases with the highest titer of 1: 896. All cases had received no injection of serum. Rising titers were found in 8 cases. The titers of Paul-Bunnell reaction had no relation with the severity of the disease.

Davidsohn's absorption test : (This was performed by the method established by the

TABLE 2. Serologic Tests in 1953

Case No.	Age	Sex	Day of Illness	Paul-Bunnell Titer	Influenzal Hemagglutination						Widal			Weil-Felix Titer (Proteus OX19)	Thymol Turbidity(Units)	Note			
					Test Titer						Titer								
					A		A'		B		S. typhosa	S. paratyphi							
						A	B												
5	12	M	16 27 52	896 896 448	256 256 1	1024 1024 1	1 1 1	<<<	128 128 1	1 1 1	160 160 160	<<<	40 40 40	80 80 80	<<<	40 40 40	1	Case of relapse 23th day after relaps:	
4	10	F	16 27 52	224 112 224	<<<	128 128 1	1 1 1		2048 4096 1	1 2 1	<<<	128 128 1	1 1 1	40 80 40	<<<	40 40 40	1		
6	9	F	9 21 45	28 56 56	<<<	128 128 1	1 1 1		1024 1024 1	1 1 1	<<<	128 128 1	1 1 1	<	40 80 80	<<<	40 40 40		1
7	11	M	8 19 44	224 224 56	<<<	128 128 1	1 1 1		256 512 1	1 2 1	<<<	128 128 1	1 1 1	80 80 80	<<<	40 40 40	<<<	40 40 40	1
8	11	M	10 21 46	112 112 112	<<<	256 256 1	1 1 1		512 1024 1	1 2 1	<<<	256 256 1	1 1 1	80 160 160	<<<	40 40 40	<<<	40 40 40	2
10	10	M	9 20 45	56 56 28	<<<	128 128 1	1 1 1		128 512 1	1 4 1	<<<	256 256 1	1 1 1	80 160 160	<<<	40 40 40	<<<	40 40 80	1
11	8	F	9 20 45	112 112 224	128 128 1	1024 1024 1	1 1 1	<	256 256 1	1 1 1	<<<	40 80 80	<<<	40 80 80	<<<	40 40 40	1	serious	
13	17	M	7 18 43	224 224 224	4076 4076 1	512 512 1	1 1 1		1024 2048 1	1 2 1	<<<	40 40 40	<<<	40 40 40	<<<	40 40 40	1		
18	11	F	9 20 45	224 448 224	256 256 1	512 512 1	1 1 1		512 512 1	1 1 1	<<<	40 40 40	<<<	40 40 40	<<<	40 40 40	2		
19	9	F	5 17 41	112 448 112	128 256 1	1024 1024 1	1 1 1		256 128 1	1 1 1	<<<	40 160 160	<<<	40 640 80	<<<	40 40 40	2		
23	17	F	2 13 38	14 448 224	2048 1024 1	512 256 1	1 1 1		512 512 1	1 1 1	<<<	160 160 160	<<<	40 80 80	<<<	80 80 80	2	slight	
21	22	F	6 17 56	56 56 2048	1024 2048 1	256 256 1	1 1 1		256 256 1	1 1 1	<<<	160 160 160	<<<	80 160 80	<<<	40 40 40	2		
21'	50	M	5 16 41	7 14 14	512	1024			2048		<<<	80 80 80	<<<	40 40 40	<<<	40 40 40	1	slight	
21''	12	M	13 24 112	56 112 112	<<<	128 128 1	1 1 1		2048 2048 1	1 1 1	<<<	40 80 80	<<<	40 40 40	<<<	40 40 40	1		
21'''	11	M	6 17 112	112 112 112	<<<	128 128 1	1 1 1	<	64 1024 16	<1 1 1	<<<	128 128 1	1 1 1	<	40 40 40	<<<	40 40 40		1
3	13	F	13 24 49	112 112 224	<<<	128 128 1	1 1 1		2048 2048 1	1 1 1	<<<	128 128 1	1 1 1	160 160 160	<<<	40 40 80	<<<	80 160 160	3

Research Committee on Infectious Mononucleosis of Japan.) Details of the techniques were as follows: Guinea pig kidney and bovine erythrocyte antigens are the same as those used by Davidsohn.¹¹⁽⁶²⁾ Techniques of agglutination were as follows: 0.5 ml of each of two absorption antigens was mixed with 0.1 ml of patient sera, and the mixture was kept at 37°C for one hour with shaking at intervals of 15 minutes. After this, it was centrifuged at 3000 r.p.m. for 20 minutes, and the supernatant fluid was diluted with buffered saline by two-fold dilution. Further procedures were the same as Paul-Bunnell reaction.

This test was carried out with sera No. 5, No. 8 and No. 21. All of them were absorbed almost perfectly by both guinea pig kidney and bovine erythrocyte antigens. However, according to the description of Minakawa and Ueyama,⁴⁸⁾ value of this examination with sera from Japanese patients are not definite.

Murata test: (A syphilitic test generally performed in Japan.) This was carried out with blood drawn on about 20th day of the illness. (See, Table 2.) The results were all negative.

(4) *Liver functional test*: Thymol turbidity tests, as shown on Table 2, were all negative on 40th to 50th day of the illness. Thymol flocculation tests made on the same date were also all negative.

4. Complication

One case of peritonsillar abscess and one case of tonsillitis were encountered a week after the onset of illness.

5. Course and prognosis in 1953

In spite of the fact that the majority of pupils recovered from fever after 2 or 3 days and attended school after 4 or 5 days, tongue signs and lymphadenoma continued for over 6 weeks. Among patients whose livers were examined by the author, there were some cases in which the liver could still be palpated on the 10th day of illness. Urobilinogen-positive cases were noticed even for more than 3 weeks. Besides, some sensitive pupils recovered gradually after one month. General languor, light or strong, seemed to have continued during this period. One case of relapse was noted in 1953. This patient, who showed the highest titer of Paul-Bunnell test, asked consultation for stomachache as a chief complaint on 15th of May, when no fever was recorded. On 7th of June, however, he relapsed with high fever and hemorrhagic rash. No fatal case was encountered. Findings of the 1954 epidemic will be stated in Chapter II.

6. Embryopathic Effects

Since a viral etiology has been presumed for this disease, it was considered of

interest to investigate whether or not congenital anomalies might be accompanied with the infection of pregnant women. It is conventional in Japan that midwives (Samba in Japanese) help delivery and only in exceptional cases special treatments by physicians are asked. On the other hand, as a mother usually is ashamed of a malformed baby, she keeps it secret and few record will be given relative to such cases. Considering these situations, the author tried to hear directly from midwives (3 in all) who were working in the village. Although it was not sure whether all pregnant mothers of this village were attended by midwives of the same village, it was believed that numbers of babies attended by them from other villages were very few. Annual numbers of birth in this village were as follows: 71 in 1950, 79 in 1951, 80 in 1952, 120 in 1953, and 115 in 1954. Numbers of the stillbirth (excluding anomalies) were as follows: 3 in 1950, 4 in 1951, 3 in 1952, 1 in 1953, and 1 in 1954. Numbers of infants with anomalies were: None during 1950-52, 1 in 1953, and 4 in 1954. One case (♀) born in 1953 with rhachischisis partialis sacralis and abdominal fissure, was excluded from the present investigations, because she was born in March. The 4 cases in 1954 consist of 1 hare lip (born on 6, November by primipara, and no case of hare lip was found in its family line), 1 anencephalia (born on 26, January), 1 polydactylia (born on 25, October), and 1 atresia recti et ani (born on 15, September). These facts appear very interesting, although no unequivocal evidence has been given as to the relationship between the increased numbers of anomalies in 1954 and the prevalence of the disease in this village. Being challenged by this, the author repeated the similar investigations during December 1955, in Shibo-Mura, Kumatsugi-Mura, Hirotani-Cho and Kamonosho-Mura. (Regarding the date of the epidemic, see Part III.) No definite results, however, were obtained in the latter areas. But this problem should deserve further investigations.

7. Treatment

To the majority of the cases, sulfathiazole, sulfadiazine and penicillin were applied, but in vain.

8. Differential Diagnosis

(a) *Influenza*: Because of the facts: 1) absence of serious disease-feeling, 2) long continuance of lymphadenoma, 3) absence of severe pharyngitis, tonsillitis, 4) existence of the tongue signs, 5) existence of liver symptoms more than lung symptoms, 6) incubation period lasting about 5 days, and also by the fact that influenza certified as A' type by the Health Research Laboratory, Hyogo Prefecture, prevailed in Hyogo Prefecture in 1953, it is sure that the present disease is different from influenza except for 1 or 2 cases which were considered to be mixed infection.

(b) *German measles*: This was excluded by the author because of the facts: that

1) characteristic rash was absent which would appear in majority, 2) lymphadenoma did not disappear within 1 or 2 weeks, 3) some cases with incubation period lasting for 5 days were found, 4) the tongue signs existed, and 5) conspicuous increase of plasma cell was absent.

(c) *Scarlet fever*: This was excluded because of the facts: that 1) characteristic rash which would appear in majority was absent, 2) pharyngitis and submaxillary lymphadenoma were not so severe as observed in scarlet fever, many of which showsodynophagia and dysmasesia, 3) duration of fever was short, 4) general lymphadenoma continued for a relatively long time without showing suppuration, 5) several cases among those diagnosed by the author had a history of suffering from scarlet fever, and 6) Downey Cells were demonstrated.

(d) *Acute infectious lymphocytosis*: This was excluded by the fact that there was no high increase of total white cell count, no appearance of lymphoblast, and existence of Downey cells.

(e) *Infectious hepatitis*: This was excluded for the reasons that there was no appearance of jaundice, and that bilirubin in urine was negative in all cases.

(f) *Izumi fever*: (Scarlatinoid, a disease first recognized by Izumi.) This can be denied by the facts: that 1) scarlatinoid rash was absent, 2) no case of the present disease had relation with specific drink and food and watery source which are believed to be origins of the illness, 3) secondary infection was very conspicuous.

(g) *Coxsackie Virus disease*: According to Uchiyama et al.,⁸²⁾ Coxsackie Virus diseases showed a significant decrease of the total white cell count. This was excluded also by the different fever type.

Measles, exanthema subitum, erythema infectiosum, typhoid fever group, endemic typhus, food poisoning, salmonella infections were also differentiated from the present disease epidemiologically, clinically, hematologically and serologically.

II. Regarding the occurrence of the disease in the second year

1. Monthly incidence

The first case diagnosed as this disease in 1954 was found on 25th, May, and monthly incidences were as follows: 2 in May; 15 in June; 33 in July; 23 in August; 21 in September; 4 in October; 6 in November; and 2 in December; with total of 106. However 21 cases found during the period from 16th of September to December will not be covered in this report, as the essential facts and conclusion would not have been altered by their inclusion. Unless specifically stated, therefore, the case numbers and numbers shown in percentage in part II, represent 85 cases found from 25th, May to 15th, September.

2. Diagnosis

In 1954, the author suspected the patients to be suffering from this disease when they had the swelling of cervical and axillary glands without having another disease.

3. Clinic

Clinical features in 1954 were almost the same as those observed in 1953, so it is thought needless to describe them again excepting the following points. The tongue signs had remarkably diminished from 100% in 1953 into 38% in 1954. Accordingly the importance of this symptom for diagnosis had been lost. On the other hand, the swelling of cervical glands which showed 24% in 1953 at the first attendance rised into 87% in 1954, and the swelling of axillary glands increased from 26% in 1953 into 86% in 1954. Therefore, these two symptoms came to have a great importance clinically. The swelling of submaxillary glands diminished from 100% in 1953 into 85%. The size of the swelling of the glands was, in many adult cases, such as to be touched as large as a thumb tip size. In the case

TABLE 3. Blood Findings in 1954

Case No.	Age	Sex	Date	Day of Illness	White Blood Cells	Eosinophils %	Basophils %	Neutro phils %			Lymphocytes %							Monocytes %	Plasma cells %	Mononucleosis %	Paul-Bunnell Titer	Note
								Stab.	Seg.	Total	Large	Small	Downey			Total						
													I	II	III							
119	27	M	July. 3	2	20,000	3	0	21	58	79	0	2	9	0	0	11	7	0	18	28		
35	14	M	July. 7		6,500	6	0	4	34	38	5	43	4	0	0	52	4	0	56	14	re-exam.	
7	12	M	July. 7		11,600	15	0	8	32	40	3	32	7	0	0	42	3	0	45	28	re-exam.	
143	23	M	July. 28	9	9,700	1	0	30	30	60	4	17	12	0	0	33	6	0	39	56		
144	6	M	July. 29	4	12,500	1	0	40	38	78	1	5	9	0	1	16	5	0	21	56	hen's egg sized	
			Aug. 14	20	11,400	5	0	25	23	48	4	29	12	0	0	45	2	0	47	28	lymphadenoma on 11/Aug.	
146	4	M	July. 28	60	10,500	9	0	4	16	20	2	46	21	0	0	69	2	0	71	224		
147	6	M	July. 28		9,300	4	0	14	29	43	3	36	8	0	0	47	6	0	53	28	re-exam.	
149	13	M	July. 30	3	8,400	0	0	23	53	76	0	14	8	0	0	22	2	0	24	112		
151	10	M	Aug. 1	1	7,900	1	0	49	25	74	1	0	16	0	0	17	8	0	25	56		
19	10	F	Aug. 2		12,800	37	0	12	20	32	3	19	5	0	0	27	4	0	31	112	re-exam.	
11	9	F	Aug. 5		12,000	52	0	6	18	24	5	12	4	0	0	21	3	0	24	56	re-exam.	
18	12	F	Aug. 5	11	7,200	11	0	20	16	36	6	16	27	0	0	49	3	1	53	224	re-exam.	
Ohshiro's 3rd girl	5	F	Aug. 6		6,900	6	0	5	37	42	34	1	4	0	0	39	13	0	52	224	re-exam.	
Ohshiro's 3rd boy	7	M	Aug. 6		9,200	4	0	6	37	43	40	0	6	0	0	46	7	0	53	224	re-exam.	
159	14	M	Aug. 7	2	4,200	2	0	29	26	55	3	5	13	0	1	22	21	0	43	28		
			Aug. 26	21	6,800	7	0	21	36	57	7	18	9	0	0	34	2	0	36	14		
164	45	M	Aug. 15	3	9,100	12	0	26	25	51	6	12	15	0	0	33	4	0	37	112		
173	38	M	Aug. 29	21	4,900	43	0	2	21	23	4	12	13	0	0	29	5	0	34	56		

of a 6-year-old child (No. 144), it was found that right submaxillary gland swelled as large as a hen's egg, and was firm and elastic at the first attendance, and diminished into the size of a thumb tip by the following day. Number of patients who complained of severe headache and lasting general languor increased remarkably in 1954. Number of the cases showing distinct Downey Cells also increased. As shown in the Table 3, titers of Paul-Bunnell reaction were 1:224 in 4 out of 17 cases, and others were lower. As to total and differential leucocyte counts, see Table 3. Results of the absorption tests will be stated later.

4. Results of the physical examinations of kindergarten and primary school children

On the physical examinations practised at a kindergarten in September, 1953, percentage of those diagnosed to be taken by this disease by both the tongue signs and the swelling of the submaxillary glands as the major symptoms, and secondly by the swelling of cervical and axillary glands, (this way of diagnose was already stated in Part 1) was 34% of 181 pupils. Results of similar examinations in July, 1954, on the same pupils who were in the first grade in a primary school, were as follows: among 192 pupils examined, the tongue signs 35%; the swelling of submaxillary glands, 93%; the swelling of cervical glands, 84%; the swelling of axillary glands, 92%; the swelling of both cervical and axillary glands, 78% (including 79% of those diagnosed to be taken by infectious mononucleosis in 1953). Thus, the swelling of cervical and axillary glands was remarkably noticed. And those exhibiting positive Tuberculin reaction were 26% in April, 1954. Physical examinations performed in June, 1954, in the kindergarten, those having the swelling of both cervical and axillary glands were 28% of 186 pupils. Among the pupils in the first grade of the primary school in 1954, only one had no swelling of lymphatic glands and the tongue signs and in the kindergarten, 17% of them did not show any of these symptoms in 1954.

5. Clinical features of the inhabitants living out of the infected districts (See Table 3 and 4, concerning age and sex.)

The first case (No. 147) came to Wada-Mura from Takamatsu, on 25th, July, 1953. The temperature was 38.7°C on 30th, July, and striking tongue signs and the swelling at both sides of submaxillary, femoral and inguinal glands was noticed. The temperature fell down on the following day and the liver was felt one finger's-breadth. The swelling of cervical and axillary glands could not be touched on 30th, 31st, during his stay in this village. Later he showed no apparent symptoms. He came to Wada-Mura again on 27th, July, 1954, and was examined on the following

day. At that time, the temperature was normal, the tongue signs was remarkable, and the swelling at both sides of submaxillary, cervical, axillary and inguinal glands was noticed, and the liver, also, was felt one finger's-breadth. But he felt well subjectively. The second and the third cases were children, 7-year-old boy and 5-year-old girl, of Dr. Ohshiro, chief of Health Research Laboratory, Hyogo Prefecture. As their symptoms in 1953, however, were described in detail in another paper,⁶⁰⁾ these symptoms have been omitted from this paper. They lived in Kobe with their parents and infected through their father, and fell ill simultaneously on 20th, June, 1953. Both of them were taken by pertussis in April, 1954. When the author examined them on 6th, August, 1954, they were very energetic, but in case of the boy, the swelling at both sides of submaxillary, cervical glands, that of left axillary, right and left inguinal and femoral glands, together with the slight tongue signs were noticed. In case of the girl, she suffered from otitis media in December, 1953, and on the author's examination, the swelling of submaxillary, cervical glands, at both sides, and that of left axillary, right and left inguinal, femoral glands were noticed together with the very slight tongue signs. In all of these three cases, the size of swollen glands was from a small finger tip size to a red bean size.

6. Cases of recurrence and re-examination (Regarding sex and age, see Tables 3 and 4, and regarding the data in 1953, case numbers are the same as indicated in Tables 1 and 2.)

(1) *Cases, which showed Paul-Bunnell titers higher than 1:224 in 1953, and showed no subjective symptom in 1954, were subjected to re-examination:*

No. 18: Fell ill on 16th, May, 1953, with cough as a major complaint, attended by the author on 20th, May, when the temperature was normal, and striking tongue signs and the remarkable swelling of submaxillary glands were found. The liver was felt one finger's-breadth. On 14th, September, suffered from the left tonsillitis, showing the temperature of 39.1°C., the tongue signs, the swelling of submaxillary and cervical glands were noticed. The liver was not felt and recovered after a few days. When examined on 5th, August, 1954, it was found, quite by chance, that the patient had been complaining of general languor, headache, nausea, and abdominal pain since 26th, July. On 5th, August, the temperature was normal, and the tongue signs, the small finger tip sized swelling of right and left submaxillary, left cervical glands, the soy-bean sized swelling of right and left inguinal, femoral glands were noticed. This was the only case showing subjective symptoms as well as positive Paul-Bunnell reaction both in 1953 and in 1954.

No. 19: Fell ill with fever on 20th, May, 1953 and attended by the author on the following day, when the temperature was 37.5°C, and the tongue signs, the swelling of submaxillary glands, and rose-spots-like rash were noticed. Later, no dis-

order was present. When examined by the author on 2nd, August, 1954, the temperature was normal, and the tongue signs, the swellings of submaxillary glands of a forefinger tip size, of cervical glands of a soy-been size, of axillary, inguinal glands of a red-been size, and of femoral glands of a soy-been size were noticed. No subjective symptom, however, was observed.

No. 11: Fell ill on 16th, May, 1953, complaining of general languor, and attended by the author on 18th, when the temperature was 38.8°C, the tongue signs, the swelling of submaxillary, cervical, and axillary glands of a small finger tip size, and of femoral glands of a red-been size, were noticed. The liver was felt one finger's-breadth. The goose-skin-like rash was noticed, and later, rheumatic pain at lower extremities was complained of. The internal hemorrhagic spots were noticed on the legs. When examined on 5th, August, 1954, the temperature was normal, the tongue signs, and the swellings of submaxillary glands of a small finger tip size, of cervical glands of a soy-been size, of axillary glands of a red-been size, and of inguinal and femoral glands of a soy-been size, were noticed, without showing any subjective symptom.

No. 7: Fell ill on 17th, May, 1953, complaining of the pain on the chest, and attended by the author on the same day, when the temperature was normal and the tongue signs and the swelling of submaxillary, and axillary glands were noticed. This case showed febricula type for about two weeks. When examined on 7th, July, 1954, the temperature was normal, and no tongue sign was noticed. The swellings of submaxillary, cervical, axillary and femoral glands of a soy-been size, of inguinal glands of a red-been size, were noticed, without any subjective symptom. Later this patient consulted the author on 21st, July, 1954, complaining of abdominal pain. At that time, it was noticeable that the tongue signs became remarkable.

(2) *Cases attended by the author both in 1953, and 1954, showing subjective symptoms, and without being subjected to hematological tests in 1953:*

No. 159: Fell ill on 20th, September, 1953, with headache and complained of general languor and abdominal pain. When attended by the author on 26th, September, the temperature was normal, the tongue signs, the swellings of right and left submaxillary, cervical glands of a small finger tip size were noticed. On 6th, August, 1954, fell ill showing high fever, and attended by the author on the following day. The temperature was 38.6°C, the tongue signs and the bilateral swellings of submaxillary glands of a small finger tip size, and of cervical, axillary, inguinal, and femoral glands of a soy-been size, were noticed. General languor lasted long.

(3) *Cases attended by the author both in 1953 and 1954, showing subjective symptoms, and without being subjected to hematological tests in both years:*

No. 121: A 16-year-old boy. Fell ill with high fever on 27th, July, 1953. When attended by the author on 29th, the temperature was 38.5°C, and the tongue signs and the bilateral swellings of submaxillary glands of a forefinger tip size, of cervical glands of a red-been size, of axillary glands of a soy-been size, and of inguinal and femoral glands of a small finger tip size were noticed. The liver was

felt one finger's-breadth. On 1st, July, 1954, fell ill again complaining of abdominal pain with vomiting and cough, and attended by the author on 4th. The temperature was normal, the tongue signs and the swellings of left submaxillary glands of a red-been size, the bilateral swellings of axillary, femoral and inguinal glands of a soy-been size, together with rose-spots-like rash, were noticed. During the early stage of the illness diarrhoea occurred.

7. On the absorption tests for the serum antibodies and Weil-Felix reaction (See, Table 4.)

Weil-Felix reaction was performed with 12 cases, and the absorption tests with 6 cases, both out of 14 patients.

(1) *Absorption tests.*

Technique: Paul-Bunnell reaction and Davidsohn's absorption test were carried out by the same method described previously. As to kaolin, animal charcoal powder, and rabbit red cells, paper by Lippelt and Nogalski⁴⁰ was consulted in the present study.

A. Absorption antigens: a) One, 2 and 20% suspensions of kaolin and animal charcoal powder dried by desicator, were made with buffered physiological salt solution (pH 7.4). b) Defibrinated rabbit erythrocytes were washed thrice with buffered physiological salt solution by centrifugation at 3000 r.p.m. The packed erythrocytes were resuspended into a 20% suspension with buffered physiological salt solution. "Boiled" rabbit erythrocytes were prepared by heating at 100°C for an hour, and adding distilled water to the original volum, and phenol at a concentration of 0.5%.

B. Method: Davidsohn's method was used, and all absorption tests was carried out simultaneously.

Result: All the tests exhibited either the type of sermsickness or normal serum, and no type of infectious mononucleosis was seen. The absorption tests using kaolin, charcoal powder, and rabbit cells did not show any fixed type of infectious mononucleosis and when compared with the table by Lippelt and Nogalski,⁴⁰ the types of the present study were supposed to belong to the type of normal serum or sermsickness.

(2) *Weil-Felix reaction.*

OX19: 3 cases showed a titer of 1:80 at the highest, and the others were lower than 1:80.

OXK: One case showed a titer of 1:80 at the highest, and the others were lower than 1:80.

OX2: One case showed a titer of 1:20 at the highest, and the others were lower than 1:20.

TABLE 4. Serologic Tests in 1954

Case No.	Age	Sex	Date	Day of Illness	Paul-Bunnell (Unabsorbed)	Absorption Antigen										Wei-Felix Titer			Note
						Boiled Bovine Erythrocytes	Boiled Guinea Pig Kidney	Kaolin			Animal Charcoal Powder			Rabbit Erythrocytes 20%					
																Un- boiled	Boiled		
								1%	2%	20%	1%	2%	20%	OX 19	OX K			OX 2	
119	27	M	July. 3	2	28											40	<20	<20	re-exam.
35	14	M	July. 7		14											<20	<20	<20	
7	12	M	July. 7		28											40	40	<20	
143	23	M	July. 28	9	56											40	40	<20	re-exam.
144	6	M	July. 29	4	56											80	40	<20	
146	4	M	July. 28	60	224	14	0	224	/	/	112	/	/	56	/	80	40	<20	
147	6	M	July. 28		28											<20	40	<20	re-exam.
149	13	M	July. 30	3	112	0	0	56	/	/	28	/	/	56	/	80	40	<20	
151	10	M	Aug. 1	1	56											<20	40	<20	
19	10	F	Aug. 2		112	28	0	112	112	28	112	112	112	112	56	40	40	20	re-exam.
11	9	F	Aug. 5		56											20	80	<20	
18	12	F	Aug. 5	11	224	0	0	224	224	224	112	112	112	56	28	20	40	<20	
Ohshiro's 3rd girl	5	F	Aug. 6		224	/	/	224	224	224	224	224	56	14	/	/	/	/	re-exam.
Ohshiro's 3rd boy	7	M	Aug. 6		224	14	0	112	112	112	224	224	224	56	56	/	/	/	
Normal	20	M	Sept. 5		56	28	0	56	56	28	28	28	14	28	28	/	/	/	contrast
Quoted from Lippelt & Nogalski (1953)			Normal serum Serum-Inj. & Viruspn. Hepatitis Inf. Monon.			(+)	+	-						(+) +					
						+	+	?						+					
						+	+	?						+					
						+	-	+						-					

8. Discussion of Part II

1. The swelling of cervical and axillary glands, which was found in many cases of the disease during the 1954 epidemic, excepting german measles, appear to be significant for infectious mononucleosis. German measles can be excluded here by the fact that some of the examined cases showed positive Paul-Bunnell reaction, as well as on the basis of the description stated previously in the section of "Differential Diagnosis."

2. At first, in view of the mode of occurrence, the author supposed that the 1954 epidemic would have been due to re-infection or re-prevalence originated from a few persons who had been in the carrier-state. But many cases might be considered to be the recurrence, because of the change of the clinical pictures, especially the facts that the tongue signs had diminished remarkably, that the swelling of cervical glands

had become the major symptom, which were compatible with other reports on epidemic occurrence of the disease, (in 1953, more than half of the cases examined showed the swelling of cervical glands after 7th day of the illness), and that some cases of the second occurrence was found out of the epidemic area.

3. Although no exact protocols were collected as to individual case showing the tongue signs and swollen glands, these symptoms seemed to begin to diminish after about three months. And the swelling of glands that was so remarkable as to give a probable diagnosis of this disease, could not be found till May, 1954, with all the patients who consulted the author. These facts suggest that the swelling of glands noticed in the present investigations had not continued from 1953, but newly occurred in 1954.

4. Only three patients consulted the author both in 1953 and 1954. Many of the patients who consulted the author in 1954 consisted of those who belonged to the same family of the patients attended by the author in 1953, and the pupils examined in the same year, both showing no subjective symptom in 1953. On the other hand, many of those who came to the author in 1953 had no subjective disorders in 1954. These facts appeared very interesting.

5. The low titer of Paul-Bunnell reaction was compatible with results obtained by Heyeraas,²⁹⁾ who stated that many borderline cases occurred on the second year and that only 4 cases out of 32 cases showed titers higher than 1:64 when examined by the original Paul-Bunnell method. None of 53 chronic cases reported by Isaacs³³⁾ showed titer more than 1:64 (although it was not certain whether the cases were epidemic or sporadic).

6. Kaufman³⁶⁾ reported 12 cases of recurrence including 7 cases of family infection. Leibowitz⁴³⁾ opposed Kaufman's view on the basis of facts that none of the cases showed high titer of Paul-Bunnell reaction both in the first and the second attacks. However, the present author found one case, as described previously, in which the high titers of Paul-Bunnell reaction were clearly demonstrated both in the first (1:448) and the second attacks (1:224).

7. Isaacs³³⁾ reported chronic cases which lasted for three months and more than four years. These cases, however, were denied by both Leibowitz⁴³⁾ and Kaufman;³⁶⁾ the former considered that they proceeded from secondary hepatitis, and the latter thought that they were owing to unexact diagnosis and improper use of the words. However, in the present author's opinion, this problem has not yet settled and should await further investigation.

8. The present author quite agrees with Kaufman³⁶⁾ who claimed that "Etiological virus may remain in the body for a few years and become activated by under physical exertion, insufficient rest, other infections, lowered resistance, or other factors."

III Prevalence in Hyogo Prefecture

A coordinated investigation carried out by the present author and the Health

Research Laboratory, Hyogo Prefecture indicated that the epidemics of this disease included the following cases besides those described previously. (See Fig. 4.) a) In 1953. In April: Shibo-Mura, Izushi-Gun.⁶⁰⁾ b) In 1954. In April: Takeno-Mura, and Nakatakeno-Mura, Kinosaki-Gun;⁴⁶⁾ Kumatsugi-Mura, Mikata-Gun; Hirotani-Cho, Yabu-Gun. In May: Kamonosho-Mura, Hikami-Gun; Fukura-Cho, Mihara-Gun; Shizuki-Cho, Tsuna-Gun. In June: Hiesho, Nishiwaki-City. c) In 1955. In June: Aogaki-Cho, Hikami-Gun.

Each of these epidemics occurred explosively among students of primary schools or lower high schools and, later, spread to whole population of the village, just in the same manner as those reported in this paper. The epidemics were distinguished from influenza by serological tests; none of the observed cases showed high titer of Weil-Felix reaction with OXK; the clinical features were similar to those described by the present author; and the highest titer of Paul-Bunnell reaction during the epidemics was 1:89.

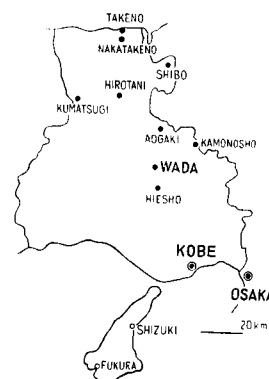


Fig. 4. Sketch of the Hyogo Prefecture, where the epidemic occurred.

Discussion

In view of the facts presented in Chapters I and II, it can be claimed that the epidemic the present author had experienced, was the prevalence of infectious mononucleosis. On the other hand, however, the findings that the author observed in his studies were not identical, in many points, with those of sporadic cases reported by other investigators. This difference made him presume in 1954,⁵⁵⁾ in the previous paper, that there might be the difference in types. Shubert et al.⁷⁴⁾ also advocated in 1954, that epidemic type should be separated from sporadic type. Further discussions will be presented here relative to this problem.

1) *Contagiousness* :

In this point, papers published already on infectious mononucleosis can be divided into five categories :

(i) Those of highly infectious: Observers of epidemic cases in the past recognized implicitly that it was highly contagious.

(ii) Those of less infectious: Evans and Robinton,¹⁸⁾ Bernstein,⁶⁾ Contratto,⁹⁾ Kasahara,³⁵⁾ Misao,⁴⁹⁾ Inoue,³²⁾ Sato et al.,⁷²⁾ etc.

(iii) Those of less infectious but recognizing the existence of epidemic cases: Glanzmann,²⁴⁾²⁵⁾ Kissel and Arnould,³⁹⁾ Rivers,⁶⁸⁾ Lawrence,⁴²⁾ Tidy,⁷⁹⁾ Downie,¹⁴⁾ etc.

(iv) Those completely opposed to the theory of epidemic occurrence, thinking that epidemic cases were not the infectious mononucleosis: Hoagland,⁸⁰⁾ Leibowitz⁴⁸⁾

who suggested it implicitly from results of serological reaction, etc.

(v) Those giving a suggestion or assertion that infectious mononucleosis should be divided into two types: Shubert et al.,⁷⁴⁾ Downey and Mckinlay,¹³⁾ Wintrobe,⁸⁹⁾ S. Oguro,⁵⁹⁾ Wechsler et al.,⁸⁶⁾ Rosenthal and Wenkebach,⁶⁹⁾ etc.

Most of reports issued before 1923 belonged to category(v). It is important to analyse outbreak when we compare the results published in the past. Outbreaks are frequent in infectious mononucleosis belonging to Kagami-Fever type. Cases reported by Kojima,⁴⁰⁾⁷⁷⁾ Yamashita,⁹⁰⁾ and others should not be regarded identical with influenza-like epidemic. The instance reported by Kojima showed one of the explosive occurrence among the students of lower high school when they were engaging in building playground. He stated in his paper⁴⁰⁾ that water of brooks or ponds or mud played a role in those epidemics. His opinion has been approved by many investigators. Yamashita⁹⁰⁾ reported an instance, in which 8 boys fell ill in the same manner during 5-7 days after bathing in a dirty river. Inoue,³²⁾ also, reported that 8 persons fell ill two weeks after eating raw grey mullet. Though not of a outbreak, the instance given by Leibowitz⁴³⁾ of falling ill 12 days after being wounded gives us interest. All these instances suggest that there must be another etiological agent of the similar nature, and that its mode of infection might be different from what supposed a so-called droplet infection. Such instances of family infection as those presented by Pfeiffer,⁶⁷⁾ Glanzmann²⁴⁾ and No. 23 case of Leibowitz⁴³⁾ are considered to be identical with those observed by the present author, when the protocols are compared carefully. So it seems true that outbreak of the similar manner with Kagami-Fever in Japan, has been occurring in Europe and America. It is thought that one of the causes to arise protean nature of this disease originated from a concept to regard these two as the same entity.

2) *Incubation period:*

Besides the epidemic cases described previously by the present author, statment by Tidy⁷⁹⁾ who experienced epidemic cases, that "I have seen fairly definite examples at 5 and at 12 days," is worthy to be noticed. Ohshiro et al.,⁶⁰⁾ also, described about epidemic case which occurred in Shibo-Mura of Hyogo Prefecture. In this case, a student of lower high school fell ill 4 days after meeting with a student of upper high school who had been feverish, and the former subsequently became the origin of an epidemic in that lower high school. It was certain that there had been no contact between these two students for ten days or so, until that day when they met together. In addition to the preceding cases given by both Halcrow et al.²⁷⁾ and the present author, in which the incubation period proved to be 5 days, those cases mentioned by Ohshiro and Tidy suggest that the incubation period is about 5 days. Although further studies are necessary to clarify this problem, the present author's opinion is that incubation period longer than five days might have been due to some misunderstanding or should have been included in sporadic cases. On the other hand, it may be supposed that the incubation period to be one or two days means the infection from the same origin. This seems true also for the case of Tidy,⁷⁹⁾ which

showed an incubation period of 12 days. Incubation periods reported by other investigators are: 10–14 days (Custer);¹⁰⁾ 4–10 days (Rivers);⁶⁸⁾ 5–10 days (Downie);¹⁴⁾ 5–15 days (Lawrence);⁴²⁾ longer than 11 days (Wintrobe);⁶⁹⁾ 7–14 days (Kasahara);³⁵⁾ 10 days (Sakamoto and Kumagai).⁷¹⁾ These data are not collected rightly, however, because they contain both epidemic and sporadic cases. Reported incubation periods of Kagami-Fever type in Japan, including results of human inoculation experiments, are: 8–13 days (Ohtawara et al.);⁶²⁾ 9–12 days (Sawada et al.);⁷³⁾ 10–17 days (Misao and Kobayashi);⁶²⁾ 7–10 days (Fukuda et al.);²²⁾ 11–16 days (Kawakita and Hosokawa).⁸⁶⁾ Most of them are around 10–14 days; this is compatible to the longer incubation period (10–15 days) in each of the reports from Europe and America as referred above. The case of wounded person given by Leibowitz⁴³⁾ which took 12 days, also show the difference between the epidemic and sporadic types.

3) *Etiological agent* :

No attempt to isolate etiological agent of infectious mononucleosis has been successful, except for those by Japanese scholars,—Fukuda et al.,²²⁾ Sawada et al.,⁷³⁾ and others as well as Misao and Kobayashi⁽⁴⁹⁾⁽⁵⁰⁾⁽⁵¹⁾⁽⁵²⁾⁽⁵³⁾ who claimed to have succeeded in isolating it from a disease of Kagami-Fever type. The author already stated that the disease of Kagami-Fever type is sporadic. However, two problems should be clarified, if one considers that this disease and sporadic infectious mononucleosis in Europe and America are of the same category: First, the diseases of Kagami-Fever type show extraordinarily high titers with OXK on weil-Felix reaction; secondly, the diseases of Kagami-Fever type are endemic and occur only in relatively restricted areas. From these points many Japanese scholars believe that the diseases of Kagami-Fever type are endemic rickettsiosis (e.g. Fukuda et al.²²⁾). But Misao and Kobayashi⁵²⁾ believe firmly that the diseases of Kagami-Fever type are identical with sporadic cases of infectious mononucleosis as found in Europe and America; their opinions are based on clinical findings (fever, lymphadenoma, mononucleosis), rising titer of Paul-Bunnell reaction in which absorption test is positive, together with their experiments in which no cross immunity is evidenced between *R. sennetsu* Misao et Kobayashi (which they claim to be the etiological agent of this disease) and *R. orientalis* s. *tsutsugamushi*, or *R. tamiyai*. These criteria given by Misao and Kobayashi are quite the same as those given by Leibowitz⁴³⁾ excepting etiology. If the titer of OXK on weil-Felix reaction of sporadic infectious mononucleosis in foreign countries is found to be high, and the same etiological agent is isolated by the same method as that taken by Misao and Kobayashi previously, then this etiological agent must be really that of sporadic infectious mononucleosis. The etiological agent of epidemic cases has not yet been established, either in Europe and America, or in Japan. The problem whether the agent may be one kind of the lymphotrope viruses of Kissel and Arnould,³⁹⁾ deserves further investigation. The possibility that “sporadic cases” of this disease are rickettsiosis and “epidemic cases” of this disease are caused by a certain kind of virus must be considered.

4) *Duration of fever :*

Pyrexia is recognized in almost all sporadic cases, and, on the contrary, is indefinite in epidemic cases. Literatures on the duration of fever manifested are as follows :—

- (i) Chiefly within one week : 4–5 days (Tidy⁷⁹⁾ ; within one week (Glanzmann,²⁴⁾²⁵⁾ wechsler et al.,⁸⁰⁾ Ohshiro et al.⁶⁰⁾ ; 3–6 days (Davis,¹²⁾ Burns⁸⁾ ; 4–7 days (West⁸⁸⁾ ; 2 days (Burnford⁷⁾ ; 1–5 days (S. Oguro⁸⁹⁾ ; 1–4 days (Torikai et al.⁸¹⁾ ; 1–5 days (39%), 10–15 days (19%) (Contratto⁹⁾ ; 5–10 days (Lawrence,⁴²⁾ Petrides⁶⁶⁾).
- (ii) Chiefly 2 weeks : 2 weeks (Sato et al.,⁷²⁾ Inoue³²⁾ ; 10–14 days (Terflinger⁷⁸⁾ ; 13–19 days (Misao⁴⁹⁾ ; 13–16 days (Fukuda et al.²²⁾ ; 5–14 days (Kasahara³⁵⁾).
- (iii) From one to three weeks : Rivers,⁶³⁾ Wintrobe,⁸⁹⁾ Bernstein.⁶⁾

It is clear that the majority of the reports on pure epidemic cases belong to the group (i), in which the duration is characteristically short. The author stated that in most cases the duration of fever lasted from one to two days, and in case of youths, seven days. A related observation by Pfeiffer⁶⁷⁾ suggests that the epidemic cases are “Drüsenfieber” as he called. Here, again, a striking difference is noticed between epidemic and sporadic cases.

5) *Hematological findings :*

It should be cited that Tidy and Daniel,⁸⁰⁾ who believed the identity of infectious mononucleosis with glandular fever stated that in epidemic cases the degree of lymphocytosis (mononucleosis) was low. Kracke,⁴¹⁾ Bernstein,⁶⁾ Halcrow et al.,²⁷⁾ Wintrobe,⁸⁹⁾ and Wechsler et al.,⁸⁰⁾ also, recognized it. Shubert et al.,⁷⁴⁾ also, thought that in many epidemic cases lymphocytosis was less than 50%, and made it a basis of his conclusion. When the results of the present author is compared with the reports by Tidy and Daniel⁸⁰⁾ and Wechsler et al.,⁸⁰⁾ it is clear that the cases which showed a mononuclear percentage higher than 50% amounted to similiary 30 to 40% of the total cases, suggesting the identity of epidemic types. As to the appearance of Downey Cells, Watson et al.,⁸⁵⁾ who studied epidemic cases, considered that a percentage more than 3% is significant for diagnosis. Likewise, Petrides,⁶⁶⁾ Wechsler et al.,⁸⁰⁾ Shubert et al.,⁷⁴⁾ as well as Leibowitz⁴³⁾ (though dealing with sporadic cases) thought that this percentage should be more than 10%. But Wechsler et al.⁸⁰⁾ stated, “We realize that many cases of infectious mononucleosis were excluded by these criteria.” In the cases of the present author a relatively few Downey Cell were noticed in the first year. This was, in the author’s opinion, due to the following facts : (a) Opportunities to take specimens repeatedly from a particular patient were limited. (b) Many cases in which the hematological observations were made, were in the earlier stages. (c) The morphological criteria adopted by the author were relatively strict, because, as mentioned above, many suspected cells were of the transitional form. The present author’s opinion is that variety of percentage of this cell in epidemic cases, as reported by various investigators, is due partially to a situation that the Downey Cell has been judged by each investigator by different standards. Leibowitz⁴³⁾ who made comprehensive studies on sporadic cases reported that the Downey Cell

appeared at 9.8 days on average, after the onset of the illness and that, in 9 out of 25 cases, it was less than 10%. His statement is considered of interest, for this shows that the morphological standard adopted by the present author for this cell is supposed to be identical with his standard, and that, regarding this cell, there is no great difference between epidemic and sporadic cases. This fact was recognized, too, by Shubert.⁷⁴⁾ Number of the Downey Cell increased in the second year, and even patients who could not be diagnosed as infectious mononucleosis clinically, had many Downey Cells. The related observation has been performed by Halcrow et al.²⁷⁾ This seemed quite true when blood film of other diseases observed prior to this epidemic, were examined as controls. Studies by Leibowitz,⁴³⁾⁴⁵⁾ Litwins,⁴⁶⁾ and others indicated that the Downey Cell was not specific for this disease. However, in epidemic cases, also, the appearance of this cell to some extent may be significant for diagnosis. But, epidemic cases cannot be denied only by the rarity or non-appearance of this cell, because the most of blood tests were carried out in early stages and the most of the patients didn't call doctors after being once examined. Downey's I type cell may be supposed to be an indicator for the reaction of lymphatic glands to various stimuli.

6) *Serological Findings :*

(i) *Paul-Bunnell reaction :*

Leibowitz⁴³⁾ stated, "A titer of 1:1792 may be accepted as diagnostic of infectious mononucleosis even without confirmation by absorption tests." But Japanese investigators hold a general view that in Japan such a high titer can scarcely be seen even in sporadic cases such as Kagami-Fever. For instance, in many observations using 0.5% of sheep erythrocytes, the highest titers were: 1:448 (Kawakita and Hosokawa,³⁸⁾ Fukuda et al.²²⁾); 1:896 (Inoue,³²⁾ Sakamoto and Kumagai,⁷⁰⁾ Sawada et al.⁷³⁾). Even in Misao's⁴⁹⁾ report which included the highest titer ever shown in Japan, the highest one was 1:3584, and even those higher than 1:1792 were very rare. When these data are compared with the table 11 by Leibowitz,⁴³⁾ it is clear that the former is lower than the latter. It is especially important that Sakamoto and Kumagai⁷⁰⁾ found the striking difference of titer between Japanese and American patients suffering from infectious mononucleosis, using the same method as those mentioned above, together with following absorption tests. Therefore, following the opinion of Sakamoto and Kumagai,⁷¹⁾ present author considers the cases positive, when they showed the titers higher than 1:224. As Shubert et al.⁷⁴⁾ described, it has been frequently reported that, in Europe and America, too, titers of Paul-Bunnell reaction were low with epidemic cases.²⁶⁾²⁷⁾⁷⁴⁾⁸⁴⁾⁸⁶⁾ And, in the present author's opinion, the types of fever tabulated by Paul and Bunnell⁶⁰⁾ seemed to be the types of fever belonging to sporadic cases. No test of Simmonds and Markowitz⁷⁵⁾ was performed, in the present study, to the author's regret.

(ii) *Davidsohn's absorption test :*

As described above, in parallel tests performed with specimens from Japanese and American patients (Minakawa and Ueyama⁴⁸⁾; Sakamoto and Kumagai⁷¹⁾), data on

Japanese patients were indefinite and irregular when compared with those from Americans. Even in America and Europe, not a few investigators are distrustful of the value of this test in epidemic cases. Even in detailed investigation by Wechsler et al.,⁸⁶⁾ the similar irregularity as seen on Japanese patients, was found. However, data by Misao,⁴⁹⁾ chiefly concerning human inoculation experiments, indicate that the titers of Paul-Bunnell reaction were rather high and a majority of the results of absorption tests was regular. This fact stands against the opinion supported by Japanese investigators on diseases of Kagami-Fever²²⁾³²⁾³⁸⁾⁷⁰⁾⁷³⁾ type as well as the observers of epidemic cases,⁵⁸⁾⁵⁹⁾ although no reason for this difference has yet been explained. If Misao's opinion is right, it may be likely that, no matter whether it be in Europe and America or in Japan, results of absorption tests must be irregular and indefinite in epidemic cases, and regularly positive in sporadic cases. Further studies are necessary, therefore, relative to these two types. And Davidsohn,^{11(b))} himself, stated, "There is reason to assume that there exist two types of infectious mononucleosis: the seropositive and the seronegative type." Based on these facts, there seems no doubt that an epidemic of infectious mononucleosis can occur, the symptoms of which quite resembled "Drüsen fieber" called by Pfeiffer. It should not be decided as Leibowitz⁴³⁾ claimed, negative cases of absorption tests are not the infectious mononucleosis. Regarding chronic cases, it appeared precarious to draw a definite conclusion only from absorption tests, because up to present time, no clear evidence has been established from the etiological point of view. At least at the present time, it seems too early to apply to the epidemic cases a strict diagnostic criterion (e. g., the appearance of Downey Cell more than 10% or mononucleosis more than 50%, positive Paul-Bunnell reaction, and positive absorption tests). This attitude may be helpful to clarify the true nature of this disease.

(iii) *Weil-Felix reaction* :

As mentioned above, the reaction with OXK showed especially high titer for Kagami-Fever type, including examples from human inoculation experiments. The reported highest titers are; 1:640 with OXK, 1:320 with OX2, 1:320 with OX19 (Misao⁴⁹⁾); 1:640 with OXK, 1:640 with OX2, 1:640 with OX19 (Kawakita and Hosokawa³⁸⁾); 1:320 with OXK, 1:20 with OX2, 1:40 with OX19 (Fukuda et al.²²⁾); 1:320 with OXK, 1:20 with OX2, 1:160 with OX19 (Sawada et al.⁷³⁾). Evans¹⁷⁾ and Wechsler et al.⁸⁶⁾ showed the cases of 1:320 with OX19, and 1:640 with OX19, respectively.

From a great discrepancy of titers with OXK as seen between the results of the present author and of other investigators on Kagami-Fever type, it is expected earnestly that the results of Weil-Felix reaction in foreign countries may be manifested more significantly on both epidemic and sporadic cases. Twelve cases with titers over 1:80 with OXK, which were reported by S. Oguro⁵⁹⁾ who investigated epidemic cases resembling those observed by the present author, are difficult to understand. However, it should be kept in mind that the infected district in Oguro's report was in Niigata Prefecture where Tsutsugamushi Disease is endemic. Therefore, it may be probable

that such high titers with OXK were due to the Tsutsugamushi infection of the past.

7) *Relapse and recurrence* :

Many investigators have considered that relapse and recurrence of this disease are rare or even practically nil.⁽⁶⁾⁹⁾³⁸⁾⁴²⁾⁵⁹⁾ Many others, however, have accepted the existence of relapse of varying degree.⁽¹²⁾²⁴⁾²⁵⁾³²⁾⁴³⁾⁶⁸⁾⁷²⁾⁸⁰⁾⁸¹⁾⁸⁶⁾⁹⁹⁾ It seems of interest that those who accept the existence of recurrence are those who dealt with epidemic cases or cases of family infection.⁽⁴⁾⁸⁶⁾⁷⁹⁾

8) *The relation between sporadic infectious mononucleosis and epidemic glandular fever* :

Baldrige et al.⁽⁴⁾ stated, "Sporadic cases are only the more marked instances of a small epidemic in which many of the cases are so mild as to escape notice." And Tidy⁽⁷⁹⁾ stated, "It is probable that the disease is infectious only in its early stages." Glanzmann⁽²⁴⁾ thought that the prevalence occurs at an interval of several years like Rubella. On the contrary to Tidy's opinion, Sakamoto and Kumagai⁽⁷¹⁾ opined that, at first, many sporadic cases occur, next comes epidemic in families, and after these two, occurs a wide prevalence, thus the contagiousness becomes more and more greater. During the earliest stage of prevalence, the present author had the same opinion as Tidy and Glanzmann, i. e., so-called sporadic cases would occur after two or three years, and that by such comprehension the doubt raised by Evans⁽¹⁸⁾ would be solved. This means that in a group with no immunity, there occurs a prevalence, and, after the immunity has been gained by many inhabitants and the etiological agents may have become more powerful by passing through human bodies, so-called sporadic cases can occur. But such situation has never been observed. Hence, the author has arrived an interpretation through investigation of the second year, as well as reviewing bibliographies, that the infectious mononucleosis should be separated into two types, i. e., epidemic and sporadic cases. It is the author's belief that this disease which has been thought of so protean nature can be more clearly understood in this way. Though it is still doubtful as to whether Attingersen's⁽³⁾ cases are identical with those reported in the present paper, Attingersen himself supposed the existence of atypical infectious mononucleosis. Shubert et al.⁽⁷⁴⁾ insisted the existence of "epidemic variant of infectious mononucleosis." Hoagland⁽³⁰⁾ claimed, "It is suggested that these epidemics may possibly be instances of a disease, or diseases, related to but not identical with infectious mononucleosis." Wintrobe⁽⁸⁹⁾ said, "It is also possible that the sporadic and the epidemic disorders are not identical." The present author proposes here to divide this disease again into two entities: "Sporadic infectious mononucleosis" and "Epidemic glandular fever," tentatively at least, until certain etiological agent or agents are identified and substantiated.

9) *To differentiate severe epidemic type and sporadic type* :

Baldrige's⁽⁴⁾ opinion, mentioned above, is a problem. No. 23 case given by Leibowitz⁽⁴³⁾ is, in the present author's opinion, a typical instance of such confusion. Moreover, if such strict serological criteria as adopted by Leibowitz are applied to diagnosis of infectious mononucleosis, no case would be found around the first recognized patient as a focus, therefore, a false sporadic case, which is really infectious

but hardly regarded to be infectious, may be observed. The present author believes that, in such an instance, if we investigate carefully, many cases which match epidemic cases, including subclinical cases, can be found around the first patient. The results of investigations by Pfeiffer and the present author showed that the severity of illness in the epidemic cases was related to the age of patient; the clinical features found in patients about 16 to 25-year-old were relatively severe and differed strikingly from those of children.

It should be emphasized here that Downey Cell, mononucleosis, or Paul-Bunnell reaction including absorption tests are nothing but indications of the disease. And, the author advocates that we should divide the infectious mononucleosis into two, namely, "Sporadic infectious mononucleosis" and "Epidemic glandular fever." This interpretation is helpful to appreciate the clinical pictures of each entity more clearly and thus to avoid confusions relative to this protean disease, and to comprehend, as a whole, the epidemic cases which really exist with high contagiousness.

Conclusion

An investigation has been undertaken on the epidemic of Infectious Mononucleosis. Its onset was first seen among primary school pupils of Wada-Mura, Hikami-Gun, Hyogo Prefecture, Japan, in the middle of May, 1953, and later spread over the entire population of the village and had recurred in 1954. Mode of infection was influenzalike. In the first year, the swelling of submaxillary glands and marked papillary proliferation of tongue were noticed as prominent signs at the first consultation. In the following year, most of the cases were considered to be the recurrence, and the swelling of cervical, axillary glands were regarded as the striking signs at the outset similar to the findings reported by other investigators. Downey Cells increased remarkably in the second year. The clinical symptoms were relatively milder in the cases of primary school pupils and elderly adults, and relatively severe in young people (about 16 to 25-year-old). Regarding the incubation period, two cases were obtained, in which it was testified to be five days. Remarkable rising of titer of Weil-Felix reaction with OXK, as found in Kagami-Fever, was not noticed in either of the occurrences of 1953, 1954. The highest titer of Paul-Bunnell reaction was 1:896 and the results of absorption tests were indefinite and irregular. The difference between epidemic cases and sporadic cases has been discussed on the points of contagiousness, incubation period, duration of fever, hematological and serological findings and recurrence. Based on the findings obtained, the author wishes to propose here to separate the disease, *again*, in agreement with the older concept of the disease, into "Sporadic infectious mononucleosis" and "Epidemic glandular fever," although the final decision should be deferred until the etiological agent or agents should be substantiated.

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