Chromosome Aberrations in Rubella Patients

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INTRODUCTION

The discovery by Nichols, et al.[1] (1962) of a high frequency of chromosome breakage in cultured peripheral blood leukocytes from measles patients, awakened an interest in the problem that many kinds of virus cause chromosome aberrations. Since then a relatively large number of reports of studies of chromosome aberrations caused by viral infections, in vivo and in vitro, has been published.

This paper presents chromosomal studies of rubella patients who had the disease during a rather large epidemic in Yamaguchi Prefecture in 1966-1967.

MATERIALS AND METHODS

The subjects were 65 rubella patients, 43 cases of boys and 22 cases of girls, ranging 4 to 15 years of age. These cases were diagnosed as rubella patients from such clinical features as mild fever, characteristic exanthem, cervical or occipital lymphadenopathy and leukopenia, and for some of them virological and serological studies were carried out.[2] Case No. 65 showed meningeal signs 3 to 4 days after exanthem and he had a high titer of neutralization antibody for rubella virus.

Chromosomal studies were carried out on samples, taken from rubella patients during the acute and convalescent periods, using a modification of the method of Moorhead, et al (1960)[3][4]. Chromosomal preparations were made with LYG-Hanks medium. Three days of culture at 37.0°C were followed by colchicine treatment for 2 hours, air drying and then staining with Giemsa solution. For each patient, 50 to 100 cells were checked for numerical and structural aberrations of chromosomes.

RESULTS

The results of the chromosomal studies on 65 rubella patients are presented in Table 1 and for the control group in Table 2. The average breakage frequency

of all rubella patients was 8.1 %, representing 380 abnormal metaphases of a total of 4686 metaphases which were checked. The average breakage frequency of control group was 4.1 %. For the patients the highest frequency of aberration was 24 % (Case No. 16).

For the control group the upper limit of breakage frequency was 7 % (4 cases), but for the rubella patients 41.3 % (28 cases) showed an average breakage of 8 % or higher. The commonest types of aberration in rubella patients were chromatid or isochromatid breaks (291/380), gaps (39/380) and fragments (47/380) with a few dicentrics (2/380), and endoreduplication (1/380) (see Table 3, and Figs. 3, 4, 5).

The distribution of breaks was random in all chromosome groups, but when considered in relation to chromosome length, breakage was somewhat higher in the longer chromosome groups, Group A being 28.1 %, Group B being 16.8 % and Group C being 41.4 %. In total, Groups A, B and C accounted for more than 80 % of the breakage with a markedly higher percentage, 71 %, of the breaks being in the long arms of the chromosomes and only 10.3 % in the short arms (Table 4).

Relatively higher breakage was found during the acute phase of the disease, with a gradual decrease during the convalescent period (Fig. 1).

All cases of rubella patients studied had a modal number of 46 chromosomes and normal karyotype, except for one case (Case No. 42, Table 1) who had 47 chromosome the additional being an extra Y chromosome making an XYY case.

Fig. 1. Distribution of Breakages during the Progress of the Disease in Rubella Patients

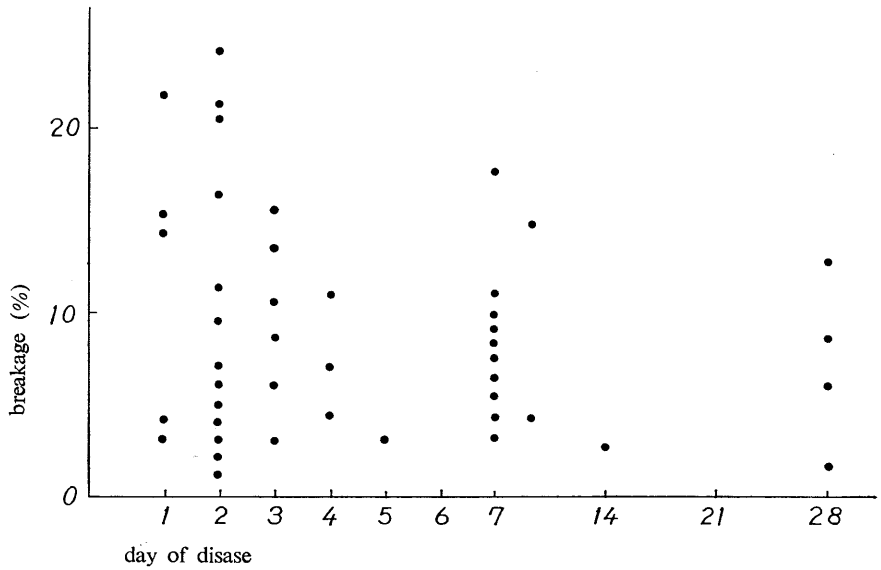

Fig. 2. Normal Karyotypes in Male and Female

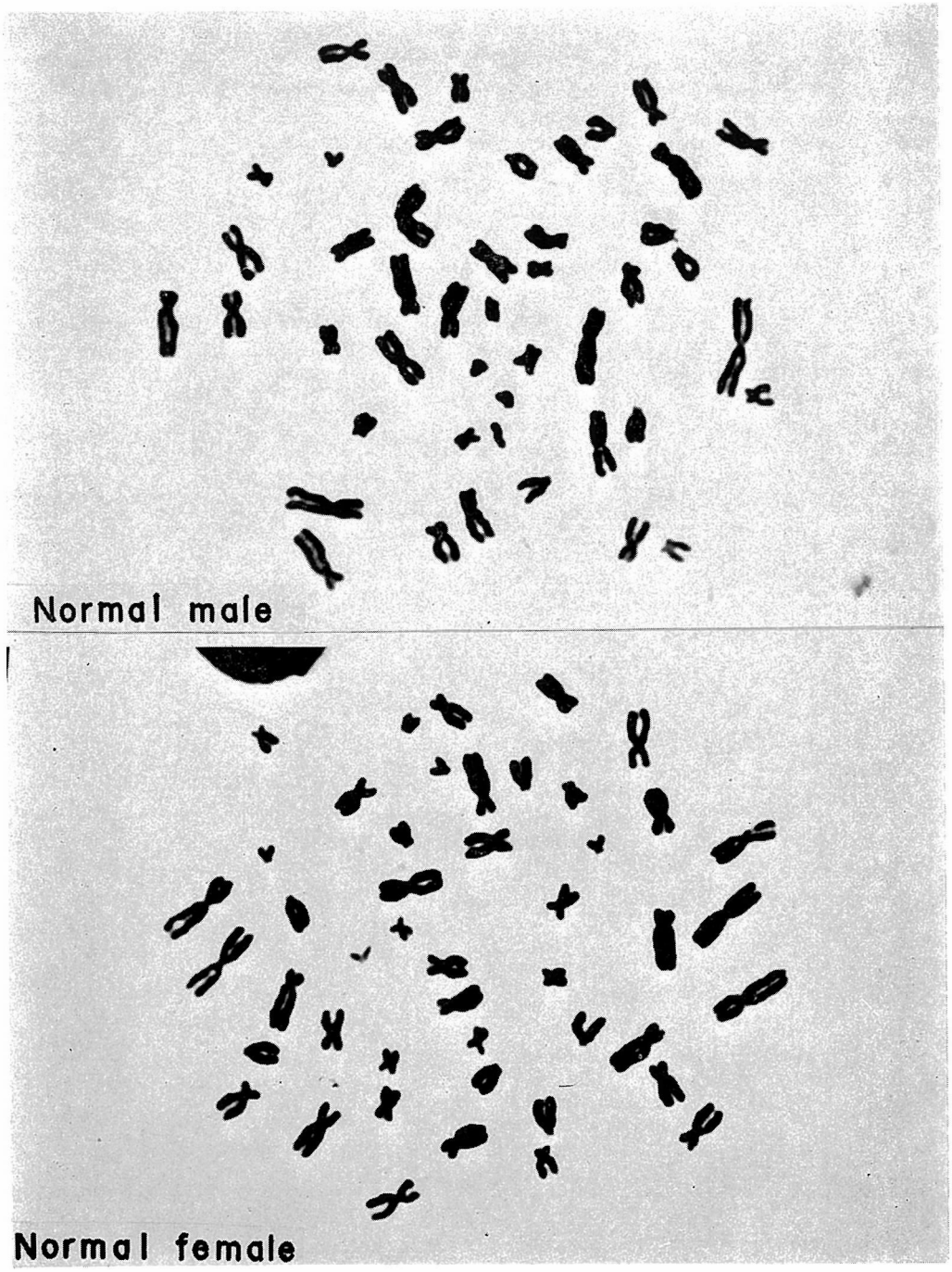

Fig. 3. Chromosome Breakages Observed in Rubella Patients (I)

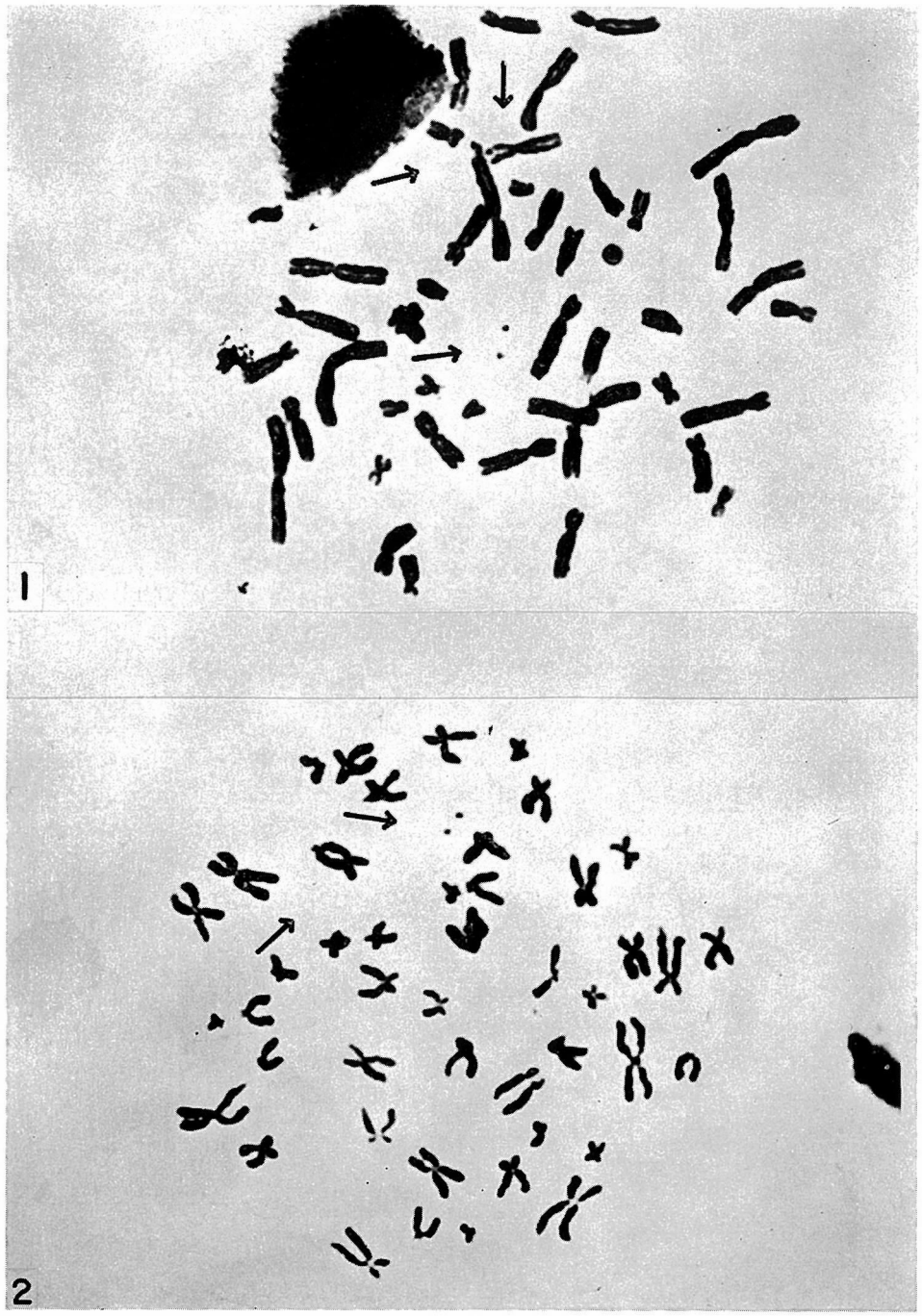

Fig. 4. Chromosome Breakages Observed in Rubella Patients (II)

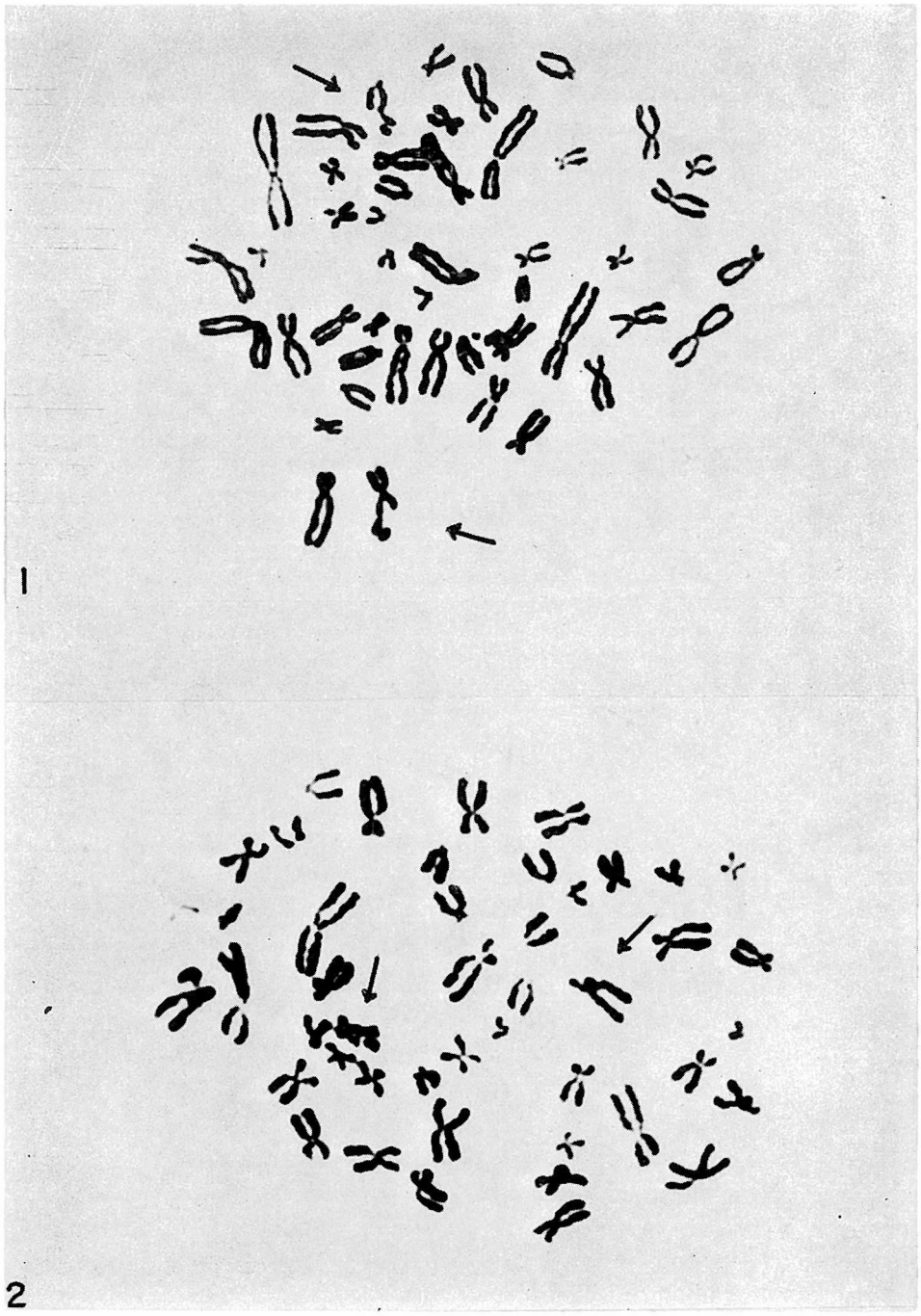

Fig. 5. Chromosome Breakages Observed in Rubella Patients (III)

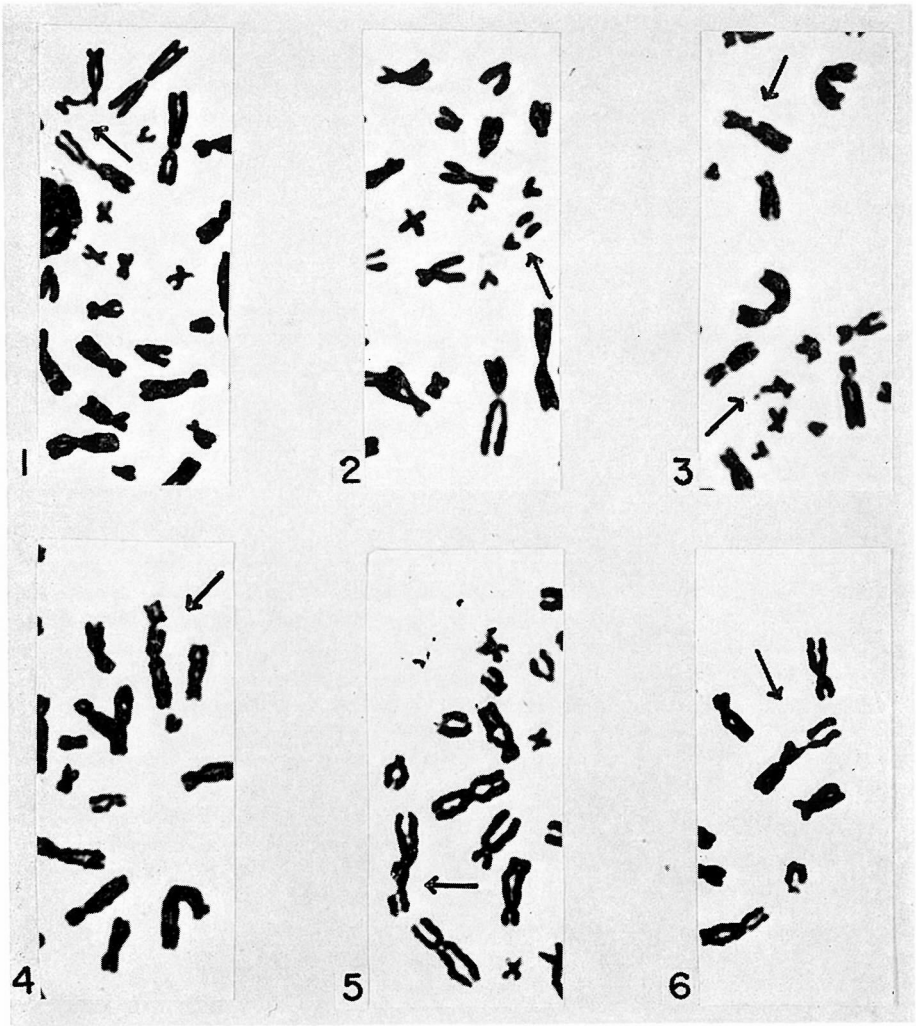

Table 1. Cytogenetical Studies on Rubella Patients

No.	Age	Sex	**Day	(%) with Breakage	No.	Age	Sex	**Day	(%) with Breakage
1	7	M	1	0	34	15	M	5	3
2	8	M	1	4	35	4	M	6	0
3	12	M	1	* 14	36	6	M	7	3
4	13	M	1	* 15	37	8	M	7	7
5	7	F	1	3	38	9	M	7	* 11
6	8	F	1	* 22	39	10	M	7	* 10
7	8	M	2	* 20	40	11	M	7	* 17
8	8	M	2	* 11	41	11	M	7	5
9	8	M	2	6	42	13	M	7	8
10	9	M	2	6	43	13	M	7	5
11	9	M	2	5	44	13	M	7	4
12	9	M	2	4	45	14	M	7	* 11
13	9	M	2	4	46	14	M	7	* 11
14	9	M	2	2	47	15	M	7	7
15	9	M	2	1	48	15	M	7	4
16	12	M	2	* 24	49	11	F	7	7
17	13	M	2	* 9	50	13	F	7	* 11
18	13	M	2	* 9	51	13	F	7	4
19	5	F	2	2	52	15	F	7	* 10
20	8	F	2	* 9	53	15	F	7	* 8
21	8	F	2	3	54	15	F	7	6
22	9	F	2	* 21	55	15	F	7	0
23	9	F	2	* 16	56	8	M	8	* 14
24	12	F	2	5	57	8	F	8	4
25	14	F	2	7	58	12	M	14	3
26	7	M	3	3	59	13	M	28	* 13
27	11	M	3	6	60	13	M	28	0
28	12	M	3	* 15	61	14	M	28	* 9
29	12	M	3	* 13	62	11	F	28	2
30	11	F	3	* 8	63	12	F	28	0
31	4	M	4	5	64	15	F	28	6
32	9	M	4	* 10	65	14	F	3	* 10
33	11	M	4	7	average for total cases				8.1 %

*higher than upper limit of control group
**the day sample checked after the onset of illness

Table 2. Cytogenetical Studies on Control Group

No.	Percentage of Breakage
1	7
2	7
3	3
4	3
5	6
6	7
7	4
8	6
9	1
10	2
11	7
12	0
13	0
14	4
15	4
average	4.1 %

Table 3. Types of Breakage in Rubella Patients

Total Number of Cells Observed	Cells with Breakages					Total (%)
	b.	g.	f.	d.	e.	
4686	291	39	47	2	1	380 (8.1)

b.: break
g.: gap
f.: fragment
d.: dicentrics
e.: endoreduplication

Table 4. Distribution of Breakages to Chromosome Group in Rubella Patients

Group	Long arm	Short arm	Undifferentiated	Total (%)
A 1 2 3	14	1	10 1 4	30 (28.1)
B	17	1		18 (16.8)
C	33	9	2	44 (41.4)
D	10			10 (9.3)
E 16 17 18		1	1	2 (1.9)
F			2	2 (1.9)
G	1			1 (0.9)
Total (%)	76 (71.0)	11 (10.3)	20 (18.7)	

DISCUSSION

The relationship between viral infections and chromosome aberrations is very important problem connected with the teratogenetic and carcinogenetic effect of viruses. During the past several years many studies concerning this problem have been reported, but chromosomal studies concerned with rubella virus have been relatively few.[5-13]

We have undertaken studies of chromosomal aberrations caused by viral diseases and we are studying experimentally various virus-chromosome relationships and interactions. We have found that various viral diseases as measles, varicella, mumps, hepatitis and aseptic meningitis induce chromosomal aberrations in peripheral blood leukocytes and we have found experimentally that breakage may be induced in many cell systems such as green monkey kidney cells, baby hamster kidney cells, the peripheral blood of green monkeys infected with rubella virus, baby hamster

kidney cells and human kidney cells infected with adenoviruses.[14)15)]

This paper presents chromosomal aberrations in rubella patients. Peripheral blood leukocytes of rubella patients showed a significantly higher frequency of chromosome breakage than the control group. The chromosome aberrations consisted mostly of simple breaks which were distributed at random in all chromosome groups. Chromosome breakage was found mostly during the acute phase of rubella and gradually decreased during the convalescent phase. These findings of chromosome aberrations in rubella patients are somewhat similar to those found in other viral diseases,[1)6)11)16-20)] but are higher for rubella than for other viral diseases so far as our studies are concerned.

The mechanism by which viruses induce breakages of chromosomes is still unknown though many studies have been carried out epidemiologically and by comparing breakages induced by neoplasms, X-rays, chemical DNA inhibitors and also using autoradiographic method. [21-23)]

SUMMARY

Chromosomal studies were carried out on peripheral blood leukocytes of sixty-five cases of rubella patients, and an increased frequency of chromosome breakages was observed. These abnormal chromosomes were mostly simple breakages such as chromatid or isochromatid breaks, gaps and fragments. These were distributed at random in all chromosome groups, but showed a higher frequency in Groups, A, B and C and were higher during the acute phase of the disease.

The fact that chromosomal aberrations were found in rubella patients, stimulates us to study the relationship between rubella virus and its teratogenesis.

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