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CHANGES IN CHROMOSOME STRUCTURES OBSERVED IN PATIENT WITH CONCOMITANT HODGKIN'S DISEASE AND MEASLES. *

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ABSTRACT: A case of a patient presenting an anatomo-pathological picture of concomitant Hodgkin's disease and Warthin-Finkeldey cells, the latter regarded as pathognomonic for measles, without clinical evidence of this infection, led us to study the chromosomal set in the patient's leukocytes. Cells with structural chromosomal aberrations (gaps and breaks) were found in a statistically significant higher frequency in relation to the control. Numerical alterations without statistical significance were also observed.

UNITERMS: Hodgkin's disease. Measles. Chromosomal aspects.

INTRODUCTION

The presence of Warthin-Finkeldey (W-F) giant cells in lymphoid tissues of the human organism, described independently by both authors in 1931, is considered pathognomonic for infection with measles, and seem to be specific reactions of the lymphoid tissue cells against the measles virus.

These giant cells appear during the prodromal phase (± 7 days after infection), and disappear soon after the onset of the rash. They contain a great number of small nuclei of a morula-or-grape-,cluster-like aspect, and are typical for elements of the lymphocytic series.

In the present case we point out the striking concomitance of the anatomo-pathological pictures of measles and Hodgkin's disease, as well as the absence of clinical manifestation of measles in the patient or in any other child in the same hospital ward. This fact seems to justify the publication of this paper although it reports only an isolated case.

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Once there is an invasion of viral agents, the measles virus in particular, an analysis of the chromosomal set of the patient seems to be appropriate to elucidate the situation, and to establish whether unbalances of the cell metabolism are actually occurring due to this virus invasion.

Generally, upon an atack by physical, chemical and biological agents, one of the cell responses becomes manifest through breakages, often restricted to the vulnerable points of the structure of the chromosomes and through structural dissarray of these elements.

Östergren and Wakonig [15], 1954, described the breakage as an anomaly of the secondary constriction in a single chromatid, or as a typical example of a secondary constriction in one chromatid accompanied by a corresponding break in the other, up to the complet breakage in both chromatids.

Ferguson-Smith et al. [3], 1962, defined the secondary constrictions as contracted regions in both chromosome chromatids, distinct from the centromere, or as a strongly marked-area of negative heteropycnosis.

These sites of secondary constrictions seem to be associated with delayed DNA replication blocks (heterochromatin) where chromosomal aberrations occur with the highest probability (Ferguson-Smith and Handmaker [4], 1961).

Ferguson-Smith et al. [3], 1962, described 20 sites of secondary constrictions, and their relative frequencies in normal human somatic chromosomes; based on this description we analysed our results.

MATERIAL AND METHODS

A 7 year-old male child (A.P.S., register n.º 732.284) of Caucasian origin, was admitted to the Serviço de Pediatria of the Instituto Central — Hospital A. C. Camargo.

Physical and lymphographic examinations showed swollen cervical and inguinal lymph nodes, some of which confluent.

Biopsies of cervical lymph nodes revealed upon histological examination a typical picture of Hodgkin's disease, and the presence of giant cells from the lymphocytic series of Warthin-Finkeldey type (1931) regarded as pathognomonic for infection with measles virus.

The global aspect of the histopathological findings were already described by Machado & Denaro (in press).

At the moment of the surgical exploration, a 10 ml sample of peripheral blood was collected in a heparinized syringe.

Chromosome preparations were obtained from 72 h leukocyte cultures, according to the modified tecnique of Moorhead et al. [10], 1960.

Concomitantly, leukocytes of a healthy individual were cultured as control under the same laboratory conditions.

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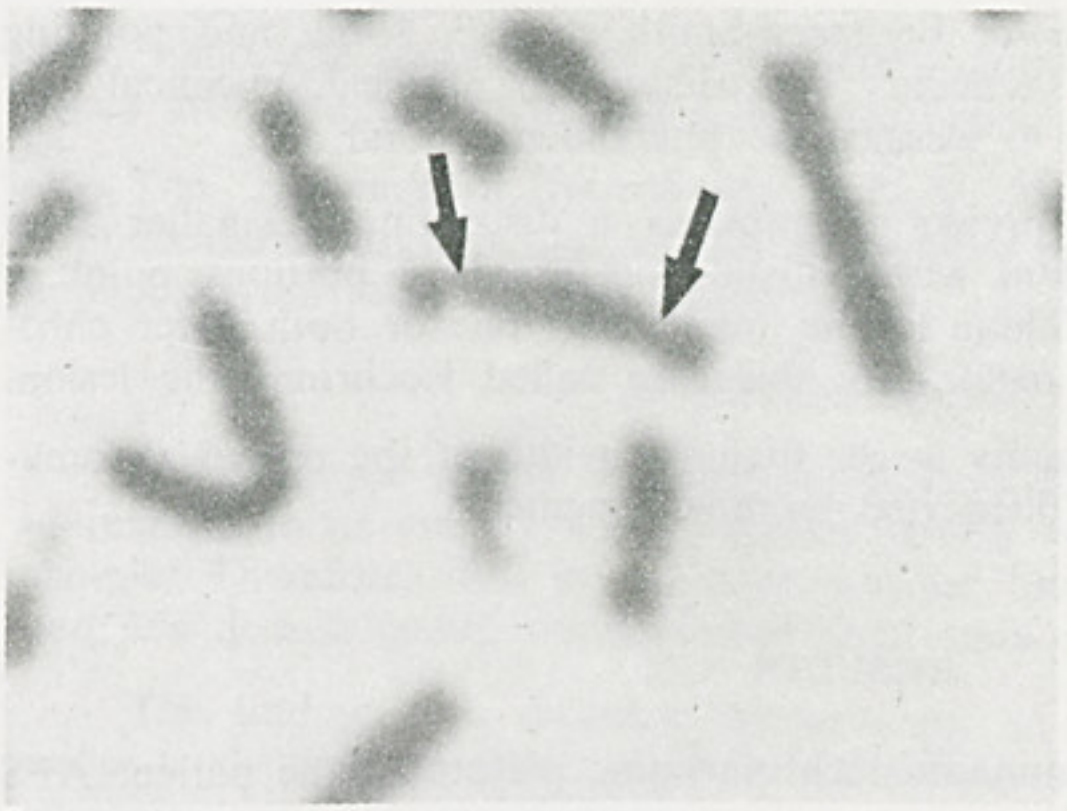

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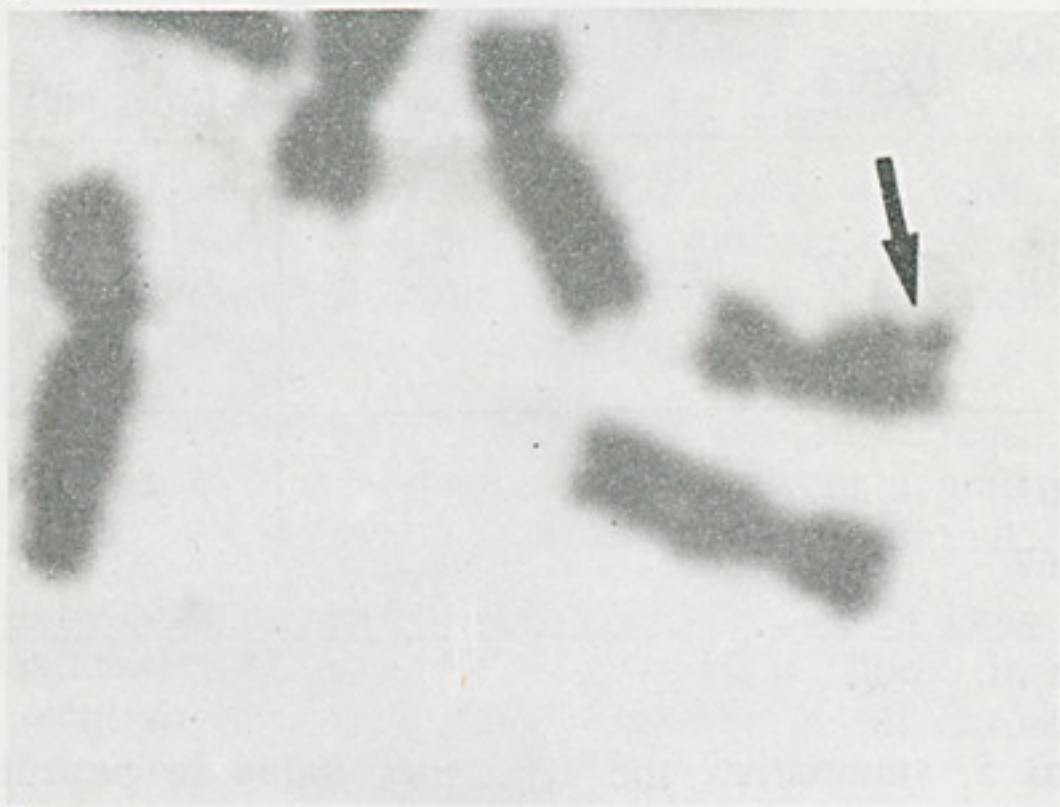

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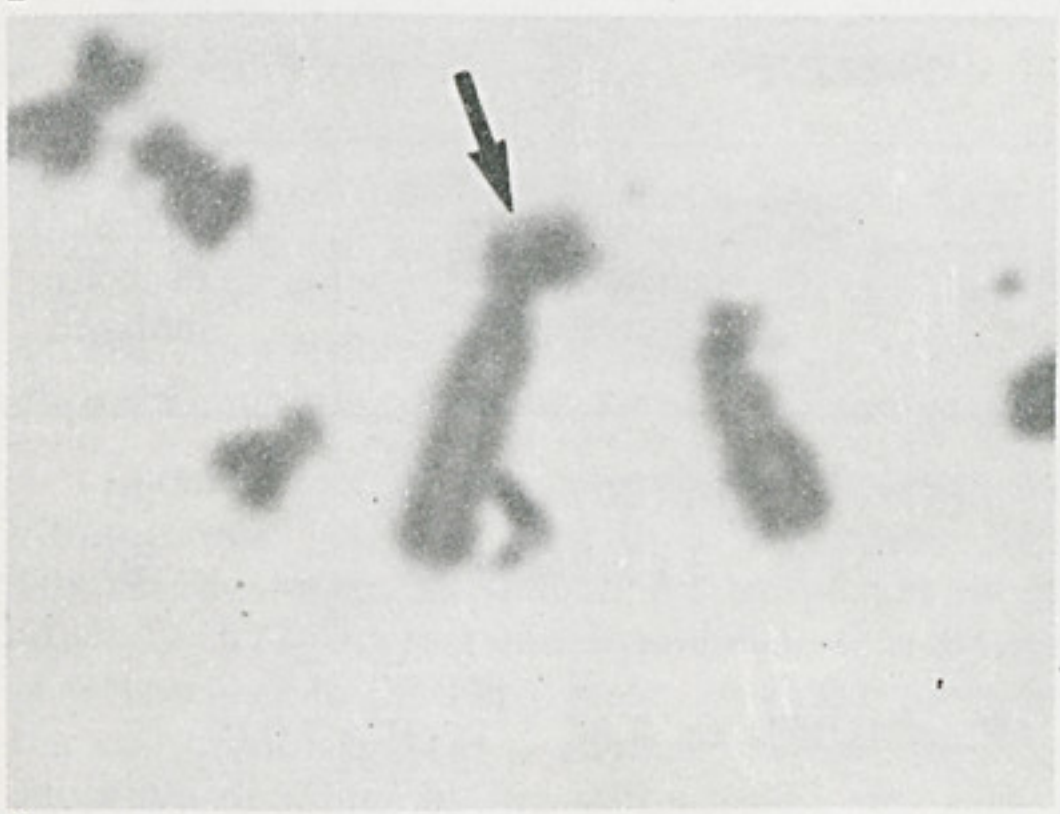

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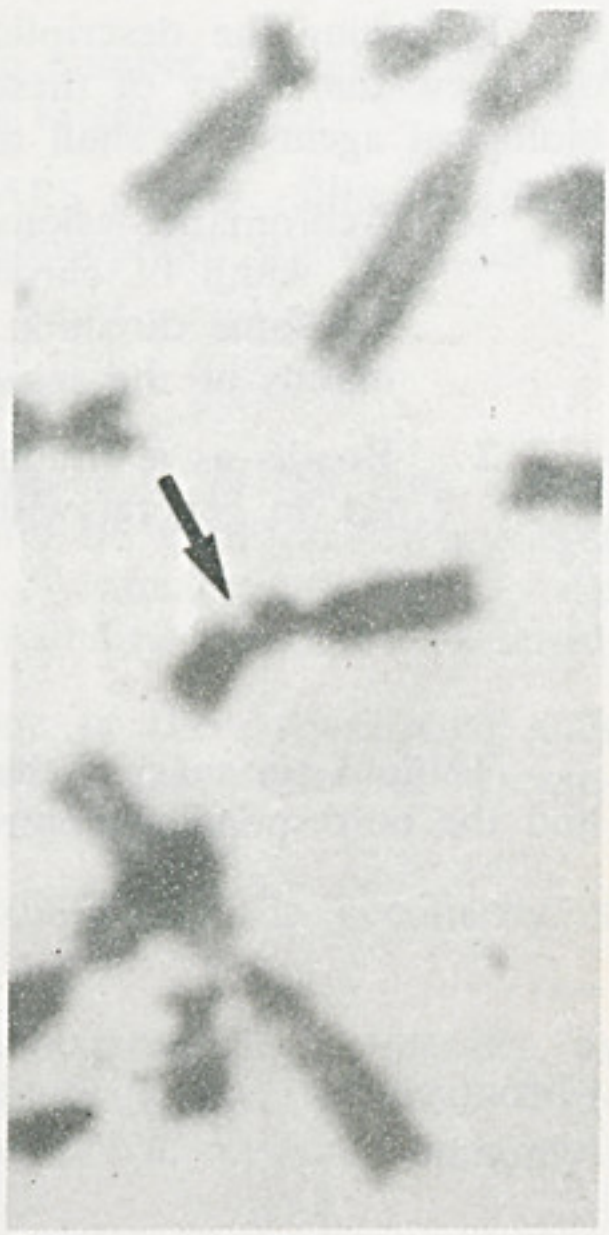

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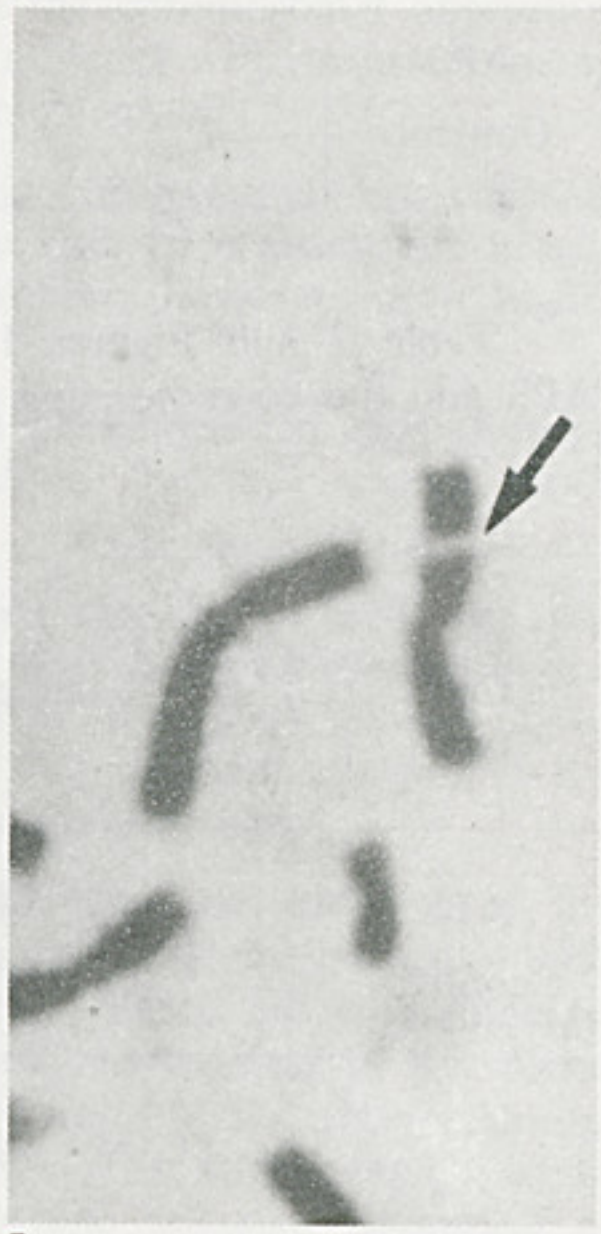

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Figs. 1 to 5 - Types of structural chromosome anomalies observed: 1 - dicentric. 2 e 3 - gap in one chromatid. 4 - break in one chromatid. 5 - break in both chromatids.

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Following the descriptions of Ferguson-Smith et al.[3], 1962, and pointing out anew the frailty of these secondary constrictions to physical, chemical and biological agents, we shall try to classify the phenomena found as:

1. Achromatic lesions, breaks or gaps as a discontinuity smaller than the width of chromatid whose distal and proximal portions point in the same direction. These lesions may affect one or both sister chromatids at the same regions, in this case called isochromatidic lesion.
2. Breaks as a discontinuity larger than the width of the proper chromatid, in general with dislocated terminal fragments.

RESULTS

Table 1 summarizes the numerical chromosome picture of the patient APS and the corresponding control.

TABLE 1

Chromosome number	45	46	47	50	80	Total of cells analysed
APS	12	63	—	1	4	80
Control	13	67	—	—	—	80

Table 2 and Figures 1 to 5, summarize, the cell types found in patient APS and the corresponding control.

TABLE 2

Cell types	normal	with structural alterations	Total of cells analysed
APS	64	16 (20%)	80
control	77	3 (3.75%)	80

$$X^2_1 = 10{,}09 : X^2_c \ (P = 0{,}05) = 3{,}84 : < P < 0{,}01$$

The results of the statistical analysis show that the difference in frequency of those breaks and chromosomal gaps is not due to chance alone. On the

other hand, the frequency of cells with hypodiploid number indicates that such losses are fortuitous in the APS patient as well as in the control.

The frequency of hyperdiploid cells in the APS patient, although higher than in the control, is not significant when the appropriate statistical test is applied. From tables of low frequencies:

$$P = 0{,}29 > Pc = 0{,}025.$$

However, the excess of hyperdiploid cells in the case of the APS patient in relation to its control (5/80 against 0/80) could be significant in a larger sample. Therefore, if it is not demonstrated that divisional faults due to the patient's disease occur, on the other hand such possibility cannot be excluded.

The finding of a dicentric chromosome in one of the hyperdiploid cells under study confirms the occurrence of breaks and possible structural rearrangements.

In view of the forementioned results, and considering the peculiarity of this case, two hypotheses can be suggested.

If we admit that the W.F. cells are really pathognomonic for measles, as Matumoto [8] (1966) and other authors claim, we would have to admit an invasion of measles agents, even through, by reasons unknown, no clinical manifestation of the disease is evident.

Gripenberg [6], 1965, points out an increase in the chromosomal aberration incidence in a lymphocyte culture from a patient affected with measles among other viral infections in relation to the normal control group.

Aula [1], 1965, reports the presence of gaps and chromosomal breakages in patients with measles, mumps and smallpox. In the case of measles, the breaks seem to be distributed at random in all chromosomes; however, in a higher frequency in the long arms.

Norrby et al. [14], 1965, described pulverization phenomena in cells showing a chromosome number higher than normal, produced by the measles viru's action.

If, on the other hand, we reject the hypothesis that W.F. cells are pathognomonic for measles, based on the absence of clinical manifestations of the disease, we would have to blame the possible causal Hodgkin's disease agent as also responsible for the presence of W-F cells and for the increase of the chromosomic aberration incidence in relation to the control group.

Aberrations of the normal chromosome model, such as doubling of the chromosome set, are described for tissue preparations from patients with Hodgkin's disease, as well as for neoplasias in general. Based on these findings, Miles [9], 1973, suggest the hypothesis of a cytogenetic progression in the oncogenesis where in the early stage, or at the moment of oncogenetic transformation, the cell would present a normal chromosomal pattern that later would lead to sucessive doubling of the chromosome set with possible selective advantage to the new population.

The presence of breaks or chromosomal gaps evidenced in preparations obtained from lymph nodes affected by Hodgkin's disease is not mentioned in

the litterature on the cytogenetics of this disease, but descriptions of marker chromosomes together with numerical aberration were given by Coutinho et al. [2], 1971, leading us to assume a previous occurrence of breaks and structural rearrangements, and consequent formation of those marker chromosomes. The fact that we did not find a significant excess of hyperdiploid cells in the APS patient does not disagree with the above findings, since the cited authors worked always with lymph nodes affected by Hodgkin's disease while we used in our study the peripheral blood of the patient. It is conceivable that the frequency of hyperdiploid cells would be much lower in the peripheral blood than in the affected nodes.

Nichols [12], 1966, believes that the possibility must be considered that any virus able to produce genetic rearrangements (activities also verified in oncogenetic viruses) could develop a carcinogenic potential if the exact karyotype for autonomy had been accidentally established. Based on these conclusions, Nichols et al. [13], 1962, and Nichols [11], 1963, point out the increase in frequency of acute lymphatic leukemia during childhood after a serious measles epidemic in Philadelphia, in 1962.

In our opinion, the fact that Hodgkin's disease patients present characteristic immunopathological defects, reinforces our admission of pathognomy of the W.F. cells for measles, since the immunological defect caused by the Hodgkin's disease picture may be responsible for the absence of clinical manifestation of measles.

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RESUMO: Num caso de paciente apresentando quadro anatomo-patológico concomitante de Moléstia de Hodgkin e células de Warthin-Finkeldey, estas últimas tidas como patognômonicas do sarampo, sem evidências clínicas desta infecção, levou-nos a estudar seu cariótipo. Células com aberrações cromossômicas estruturais (falhas e quebras) foram encontradas com freqüência significativamente maior em relação ao controle. Alterações numéricas sem significância estatística foram também observadas.

UNITERMOS: Moléstia de Hodgkin. Sarampo. Aspectos cromossômicos.

REFERENCES

1. AULA, P. Virus-associated chromosome breakage. A cytogenetic study of chickenpox, measles and mumps patients and of cell cultures infected with measles virus. *Acad. Sci. Fennicae, 89,* 1965.

2. COUTINHO, V.; BOTTURA, C. & FALCÃO, R.P. Cytogenetic studies in malignant lymphomas: a study of 28 cases... *Brit. J. Cancer, 15:* 789-801, 1971.

DENARO, L.; MACHADO, J.C. & MARTINS, Y.R. Changes in chromosome structure observed in patient with concomitant Hodgkin's disease and measles.
Mem. Inst. Butantan, 39: 225-231, 1975.

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3. FERGUSON-SMITH, M. A.; FERGUSON-SMITH, M. E.; ELLIS, P. M. & DICKSON, M. The sites and relative frequencies of secondary constrictions in human somatic chromosomes. *Cytogenetics, 1:* 325-343, 1962.

4. FERGUSON-SMITH, M. A. & HANDMAKER, S. D. Observations on the satellited human chromosomes. *Lancet, I*(7178): 638-640, 1961.

5. FINKELDEY, W. Über riesenzellbefunde in den Gaumennandelm zugleica un Beitrag sur Histopathologie der mandelveränderungen in maser ninkubations stadium. *Wirc. Arch. Path. Anat., 281:* 323, 1931.

6. GRIPENBERG, U. Chromosome studies in some virus infections. *Hereditas, 54:* 1-18, 1965.

7. MACHADO, J. C. & DENARO, L. Relato e considerações sobre a presença de células de Warthin-Finkeldey em paciente portador de Moléstia de Hodgkin em atividade. *Mem. Inst. Butantan* (no prelo).

8. MATUMOTO, M. Multiplication of measles in cell cultures. *Bact. Rev., 30:* 152-176, 1966.

9. MILES, C. P. Chromosomes changes in Hodgkin's disease. International Symposium on Hodgkin's Disease. *Nat. Cancer Inst. Monogr., 36:* 197-201, 1973.

10. MOORHEAD, P. S.; NOWELL, P. C.; MELLMAN, W. J.; BATTIPS, D. M. & HUNGERFORD, D. A. Chromosome preparations of leukocyte culture from human peripheral blood. *Exp. Cell Res., 20:* 613-616, 1960.

11. NICHOLS, W. W. Relationships of viruses, chromosome and carcinogenesis. *Hereditas, 50:* 53-80, 1963.

12. NICHOLS, W. W. The role of viruses in the etiology of chromosomal abnormalities. *Amer. J. hum. Genet., 18:* 81-92, 1966.

13. NICHOLS, W. W.; LEVAN, A.; HALL, B. & CATERGREN, G. Measles. Associated chromosome breakage. *Hereditas, 48:* 367-370, 1962.

14. NORRBY, E.; LEVAN, A. & NICHOLS, W. W. The correlation between the chromosome pulverization effect and other biological activities of measles virus preparations. *Exp. Cell Res., 41:* 483-491, 1965.

15. ÖSTERGREN, G. & WAKONIG, T. True or apparent sub-chromatid breakage and the induction of labile states in cytological chromosome loci. *Bot. Not.,* : 357-375, 1954.

16. WARTHIN, A. S. Occurence of numerous large giant cells in the tonsils and pharingeal mucosa in the prodomial stage of measles. *Arch. Path., 11:* 864, 1931.

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