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Are Oocytes Formed and Used Sequentially in the Mammalian Ovary? [and Discussion]

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Are oocytes formed and used sequentially in the mammalian ovary?

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(*MS. received July* 1969)

[Plate 12]

Female foetuses normally possess at birth, or soon after birth, their total stock of a million or so oocytes. These oocytes are in dictyotene and await the required hormonal stimulus during adult life for further development leading to ovulation. The situation in the male differs for the spermatogenic cells increase greatly in numbers through mitosis in neonatal and adult life.

It is intriguing to know whether there is any regularity in the migration of germ cells into the gonad, in the utilization of oocytes in the adult female or in the mitotic rate of different spermatogenic cells in the testis. Data on differential mitotic rates in spermatogonia are reviewed by Ford in this meeting (see p. 53). Some recent results of Dr S. A. Henderson and myself indicate that there is a considerable degree of order in the formation and use of oocytes in the adult female, their ovulation following a sequence determined somewhere during foetal development (Henderson & Edwards 1968; Fowler & Edwards 1969).

Before discussing our data, however, it is worthwhile mentioning the evidence for factors that regularly interfere with germ-cell migration and proliferation. These factors include the genotype of the foetus (Mintz 1960) and the administration of drugs to the mother (Hemsworth & Jackson 1962; Hemsworth 1968). In mice homozygous for certain genes, or with various genotypes, germ cells can be totally or partially obliterated. Injection of various alkylating agents into the mother can likewise deplete or destroy the germ cells. There can be different consequences for the two sexes after partial depletion of the germ cells. Effects in the male may be wholly or partially alleviated by spermatogenic mitosis in the post-natal and adult period. In the female the effects are more pronounced in the adult, for the limited period of mitosis in the foetus does not permit full repopulation of germ cells. Some human conditions leading to female infertility may be due to depletion of germ cells.

More pertinent to my theme today is the embryological evidence that germ cells enter the foetal gonad, and initiate their development, in a regular order. In *Macaca mulatta* and human foetal ovaries, for example, oocytes at the cortico-medullary boundary are always the earliest to enter successive stages of development (van Wagenen & Simpson 1965). In the perimedullary region, oogonia enlarge first, meiotic prophase begins first, and the earliest primordial follicles are formed there. The embryological evidence indicates, therefore, the presence of a 'production line' of oocytes even at this stage of development. The initial plan might have been determined earlier: even at or before the stage when the germ cells entered the germinal ridge. There is thus a sequence of developing oocytes in the foetal ovary, the oocytes at various stages in the sequence being joined in groups by cytoplasmic bridges as described by Dr Peters at this meeting (see p. 91).

Our evidence indicates that a similar kind of sequence exists in the utilization of oocytes in the adult. To determine their order of utilization, distinct markers are required which can

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first be recognized in oocytes as they are formed in the foetus and then as they are ovulated in the adult. Fortunately, such markers have been provided naturally. The early stages of meiosis between leptotene and diplotene occur in the foetus; chiasma formation and genetic recombination thus occur at this time. Recombination of genes thus provides a marker for the foetus (figure 1). The oocytes enter and remain in diffuse diplotene (dictyotene) during the growth of the mother and diakenesis occurs after the LH surge in mid-cycle just before ovulation. In diakinesis the chiasmata in oocytes can be counted easily (figure 2, plate 12), and the chiasma frequency thus provides a marker in the adult. Obviously, recombination and chiasma frequencies are closely related phenomena (figure 1).

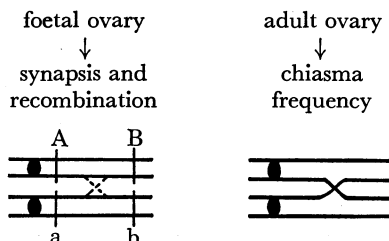

FIGURE 1. Relationship between genetic recombination in oocytes of the foetal ovary and the appearance of chiasmata in oocytes in the adult ovary. The illustration shows one chromosome with one chiasmata.

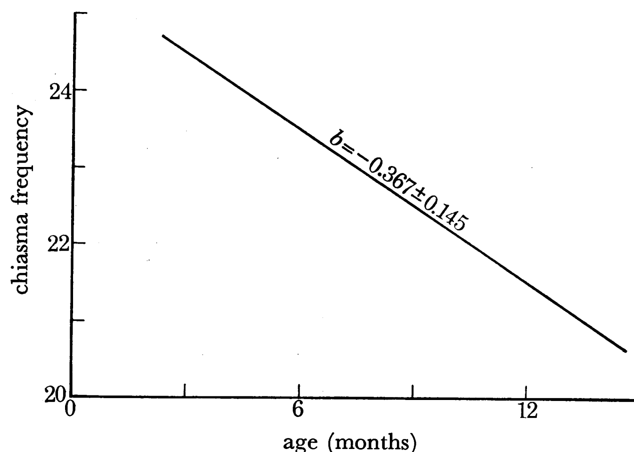

FIGURE 3. Relation between chiasma frequency in oocytes and maternal age in CBA mice. The regression coefficient is highly significant. The decline in chiasma frequency with age was less marked in C57 BL mice. Figures 1 and 3 are reproduced by permission of the Editor of *Nature*.

The number of chiasmata were counted in oocytes taken from mice of increasing maternal age (figure 3). The mean declined with maternal age, especially in CBA mice. Clearly there is some form of progression during the utilization of oocytes as the mother ages, as shown by this progressive decline. But which sort of progression could produce such a decline?

One cause could obviously be due to changes in the oocytes as they themselves grow older in the mother. But this possibility can be excluded by considering the evidence available on genetic recombination in relation to maternal age. In mice the recombination frequency of linked genes declines with maternal age (Bodmer 1961; Reid & Parsons 1963). This decline in recombination cannot be due to ageing of the eggs because recombination took place during early meiosis in the foetus. In other words, oocytes with low recombination frequency are ovulated towards the end of the mother's life.

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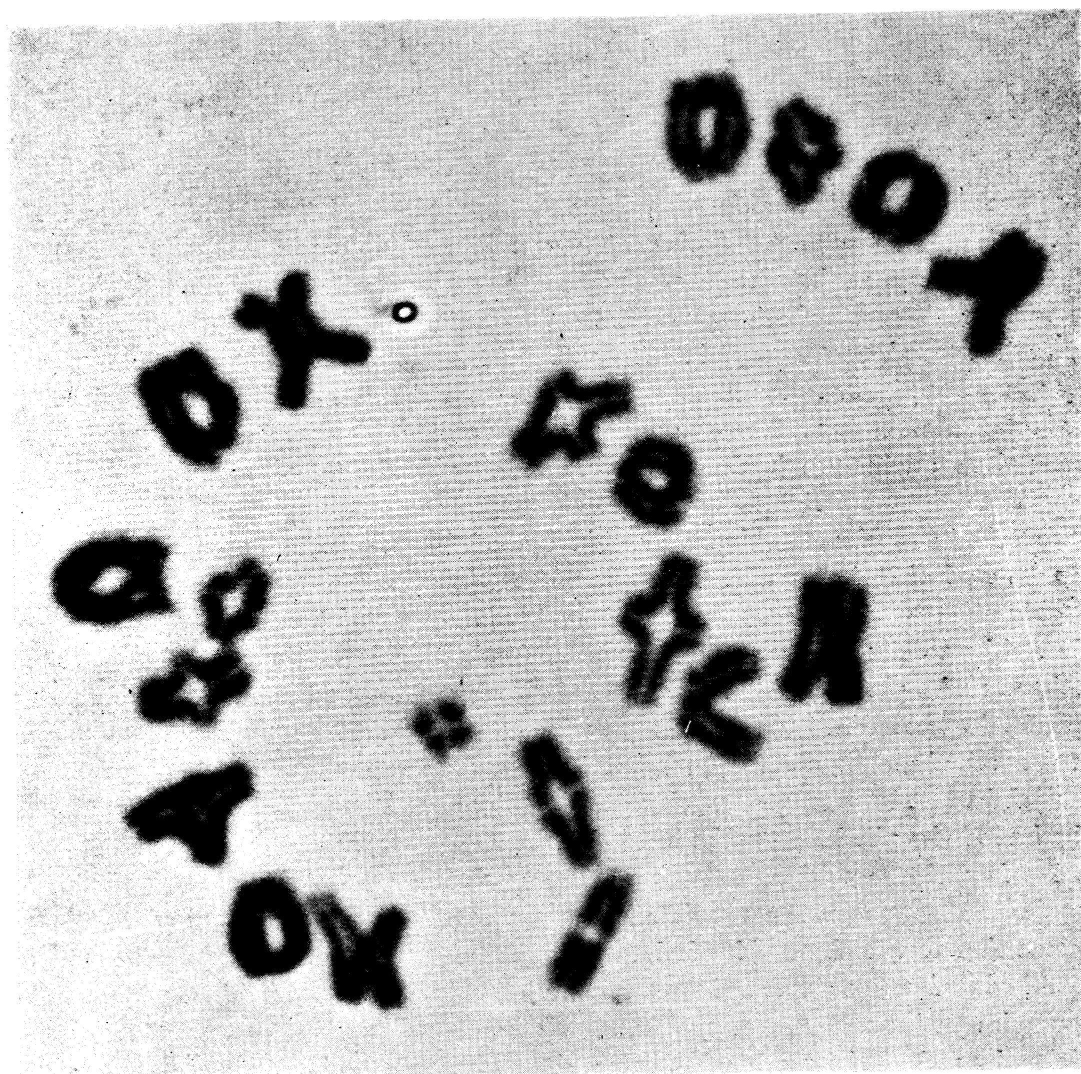

FIGURE 2. Diakinesis in an oocyte from a 6-month-old CBA mouse. The individual chromatids can be seen; eight chromosomes have two chiasmata each, and 12 have one chiasma. Total, 28 chiasma.

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Taken together, the decline in both chiasma and recombination frequency with increasing maternal age are complementary, and confirm the sequential use of oocytes in adult mice. This sequence could clearly be based on that demonstrated embryologically during earlier stages of germ-cell and oogonial development in the foetus. Moreover, parallels can be drawn with similar sequences in other organisms, e.g. the anther of the rye plant. There, too, a production line exists from one end of the anther to the other, and the chiasma frequency is found to change as the pollen grains mature in a similar manner to oocytes of the mouse (Rees & Naylor 1960). Alterations in chiasma frequency along the anther are evidently determined by the relation between nutrient supply and position of pollen grain in the anther, grains with higher frequency occurring in those parts with the better supply.

The situation in the male mammal is quite different to that in the female. Meiosis takes place throughout adult life; recombination and chiasma frequencies will thus measure events occurring just before the production of spermatozoa in the adult and will not provide an indication of foetal events. Our studies showed that the chiasma frequency rose slightly with advancing paternal age (Henderson & Edwards 1968), and it is of interest that recombination frequency also increased slightly (Bodmer 1961; Reid & Parsons 1963). The factors responsible for this slight increase have not been analysed.

Clearly, more rigorous tests are required to analyse the sequential use of oocytes, including for example the selective labelling with tracers of those oocytes formed last in the foetus. Meanwhile, our model serves as a guide indicating the orderliness of the formation and use of oocytes in mammals.

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Discussion on papers by H. Peters, p. 91 *and R. G. Edwards, p.* 103

A. K. Tarkowski: There is a general belief that in the mouse, primordial germ cells originate in the yolk sac. However, according to Ozdzenski (1967 *Zool.* **17**, 367–379), the first germ cells appear before the somites are formed, in the embryonic rudiment of the allantois which is continuous with the primitive streak. Germ-cell formation occurs over a period of time, even as late as in embryos with a few somites, and during this period they can be found both in the allantoic rudiment and in the primitive streak. The location of germ cells in the endoderm is undoubtedly secondary. The earliest human embryo described by Witschi, with germ cells in the endoderm of the yolk sac, was already in the 12-somite stage, i.e. at the stage by which all primordial germ cells in the mouse have also been located in the endoderm.

A. McLaren: Has any stage been identified during primordial germ-cell migration in mammals which shows the typical pinocytosis effect as described by Dubois in the chick?

H. Peters (*The Finsen Laboratories, Copenhagen*): No information exists on these points.

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A. McLaren: Are there more data on the decrease in recombination with age? The data of Fisher on the region of chromosome 5 between *undulated* and *Agouti* showed that a strong and highly significant decline with age occurred but to the same degree in both sexes (Fisher 1949 *Heredity* **3**, 229).

R. G. Edwards: The exact relationship between recombination frequencies of two genes is related to their site on the chromosome and position of the chiasmata. Recombination frequencies in a chromosomal region might rise, even though the overall tendency was for a decline in number of chiasmata. The linkage group between *pallid* and *fidget* is a long one. Critical data using a number of linked genes are required for fine analysis and chromosome 5 of the mouse is currently being analysed for this purpose.

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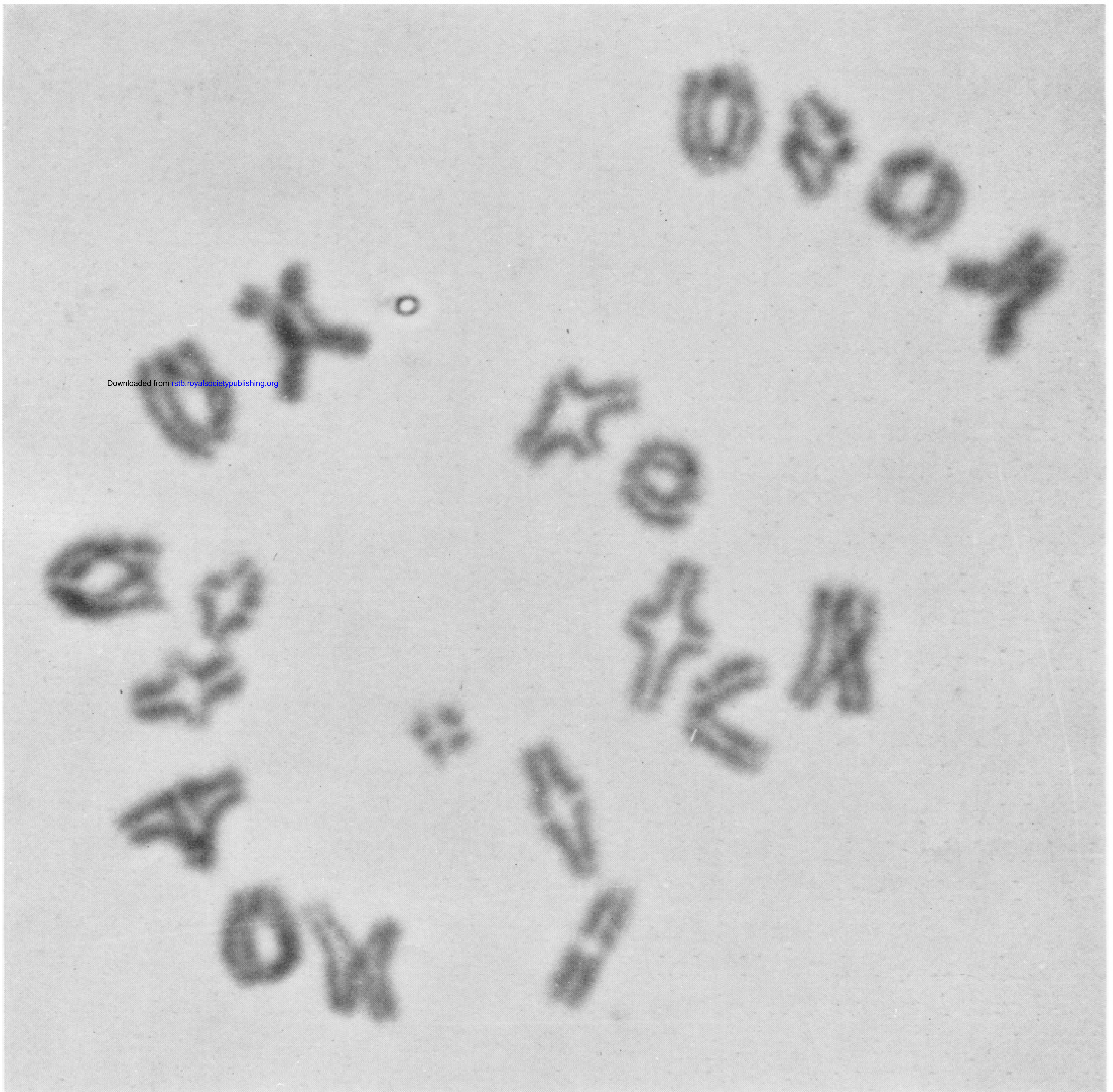

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