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The Chromosome Abnormality in Mongolism

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ABSTRACT

In an examination of our present knowledge regarding chromosome anomalies in mongolism the anomalies of trisomy-21 (the commonest anomaly in association with mongolism), 13-15/21 translocation and 21-22/21 translocation were illustrated and discussed. The relatively uncommon chromosome translocations and chromosome mosaicisms found in association with mongolism have especial clinical importance. Translocation of either type may occur as an isolated finding in a mongoloid patient. However, the translocation chromosome is frequently also found in one of the phenotypically normal parents. This is associated with an increased incidence of mongolism in the offspring, though the actual risk figure is uncertain in view of the small number of families described to date. The occurrence of chromosome mosaicism in mongolism may be associated with incomplete manifestation of the syndrome, and the ultimate mental development in such patients has varied from normal to severely retarded in cases described in the literature.

IN 1932, Waardenburg suggested that mongolism might be associated with the presence of an extra chromosome (quoted by Penrose[1]). It was not possible to test this hypothesis until improvements in tissue culture techniques permitted the accurate counting of human chromosomes and the establishment of the normal human chromosome number in somatic cells as 46.[2] Using these new techniques, Lejeune, Gauthier and Turpin[3] demonstrated the presence of an extra small chromosome in nine cases of mongolism. This finding was confirmed by other workers.[4, 5] Soon after this discovery, cases were described in which the extra chromosome, instead of being free, was "attached" to another chromosome of the cell.[6, 7] Yet other cases have been described in the last year in which the cells of the suspected mongol patient were found to be a mixture of normal cells and others containing the extra chromosome. In the first of the latter patients to be described the diagnosis of mongolism was in doubt, presumably on account of the presence in the body of normal cells.[8]

TRISOMIC MONGOLS

In the normal somatic cell, there are 22 pairs of non-sex chromosomes or autosomes and a pair of sex chromosomes. The latter are similar in appearance in the female (XX) and resemble the larger members of the 6-12 group of autosomes. In the male, there is only one X chromosome, the other sex chromosome (Y) resembling the 21-22 pairs of autosomes.

If an additional chromosome is present so that there are three matched chromosomes instead of the usual pair, the individual is said to be trisomic for this chromosome. This is the situation in the majority of cases of mongolism, such patients being trisomic for one of the two smallest pairs of autosomes (Fig. 1). Whether the trisomy is of chromosome 21 or 22 is not absolutely certain, but it is usually considered to be 21 and will be so described in this paper. The extra chromosome probably arises owing to a process known as non-disjunction occurring in the germ cells. During normal meiosis, the homologous chromosomes become approximated and then separate, so that each germ cell contains half the number of chromosomes found in somatic cells (i.e. 23). If, instead of separating in

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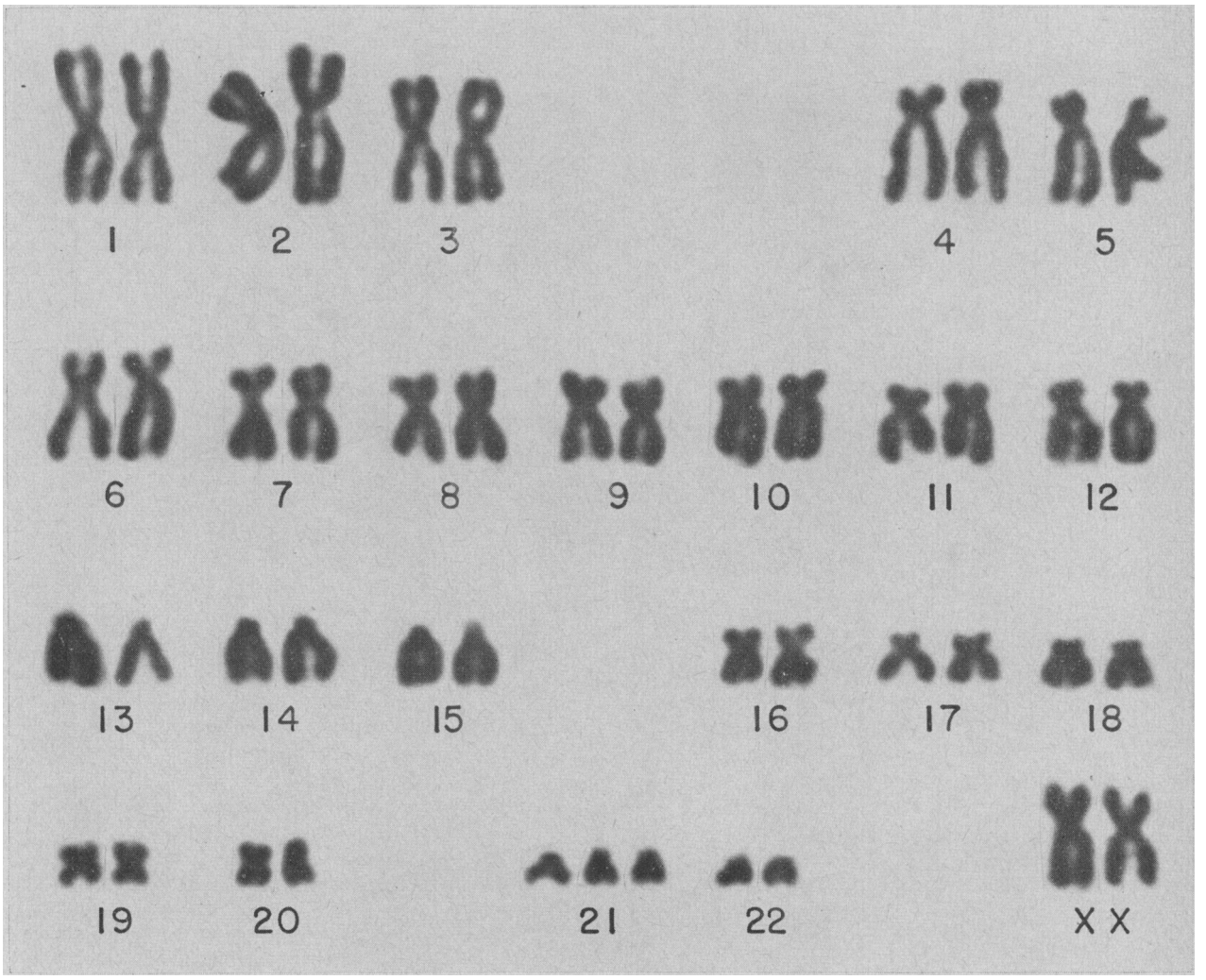

Fig. 1.—Trisomy of chromosome 21, the commonest chromosome anomaly seen in mongolism.

the normal fashion, both members of the pair pass into one cell, this cell will contain 24 instead of 23 chromosomes. This failure of normal separation is known as non-disjunction and on fertilization will yield a trisomic individual. Owing to the association of increased maternal age with mongolism, the non-disjunction probably occurs in the division of the ovum. This type of abnormality, trisomy of chromosome 21, is found in the majority of cases of mongolism.

TRANSLOCATION IN MONGOLISM

In a minority (perhaps 5%) of cases of mongolism, the extra chromosome is not free in the cell but "attached" to another chromosome (Fig. 2). The "attachment" involves the loss of a small fragment from the ends of the chromosomes, followed by the translocation of one on to the other. Translocations of the 21 chromosome take place on to a member of the 13-15 group or on to another 21 or 22 chromosome. The former is perhaps the commoner type of translocation.

The translocation of chromosome 21 on to one of the members of the 13-15 group may occur in sporadic cases of mongolism[1, 6] or in families with more than one case of mongolism.[9-14] The importance of the latter cases is that the translocation chromosome is carried by one of the normal parents and may pass through several generations. Mr. F. Sergovich, a graduate student in the Department of Microscopic Anatomy, University of Western Ontario, is currently studying several such families, and I am grateful to him for the karyotype shown in Fig. 3. In these clinically normal carriers, the chromosome count is reduced to 45, as there is only one free chromosome 21 (the other being translocated on to a member of the 13-15 group). These carriers have a virtually normal genetic complement, except for the loss of small chromosome fragments from the two chromosomes involved in the translocation.

The behaviour of the translocation chromosome and the two normal homologues (the free chromosome 21 and the unpaired member of the 13-15 group) during meiosis determines the chromosome complement of the germ cells (ova or sperms). There are eight possible chromosome complements in the germ cells of the carriers of a translocation

Canad. Med. Ass. J.
Sept. 1, 1962, vol. 87

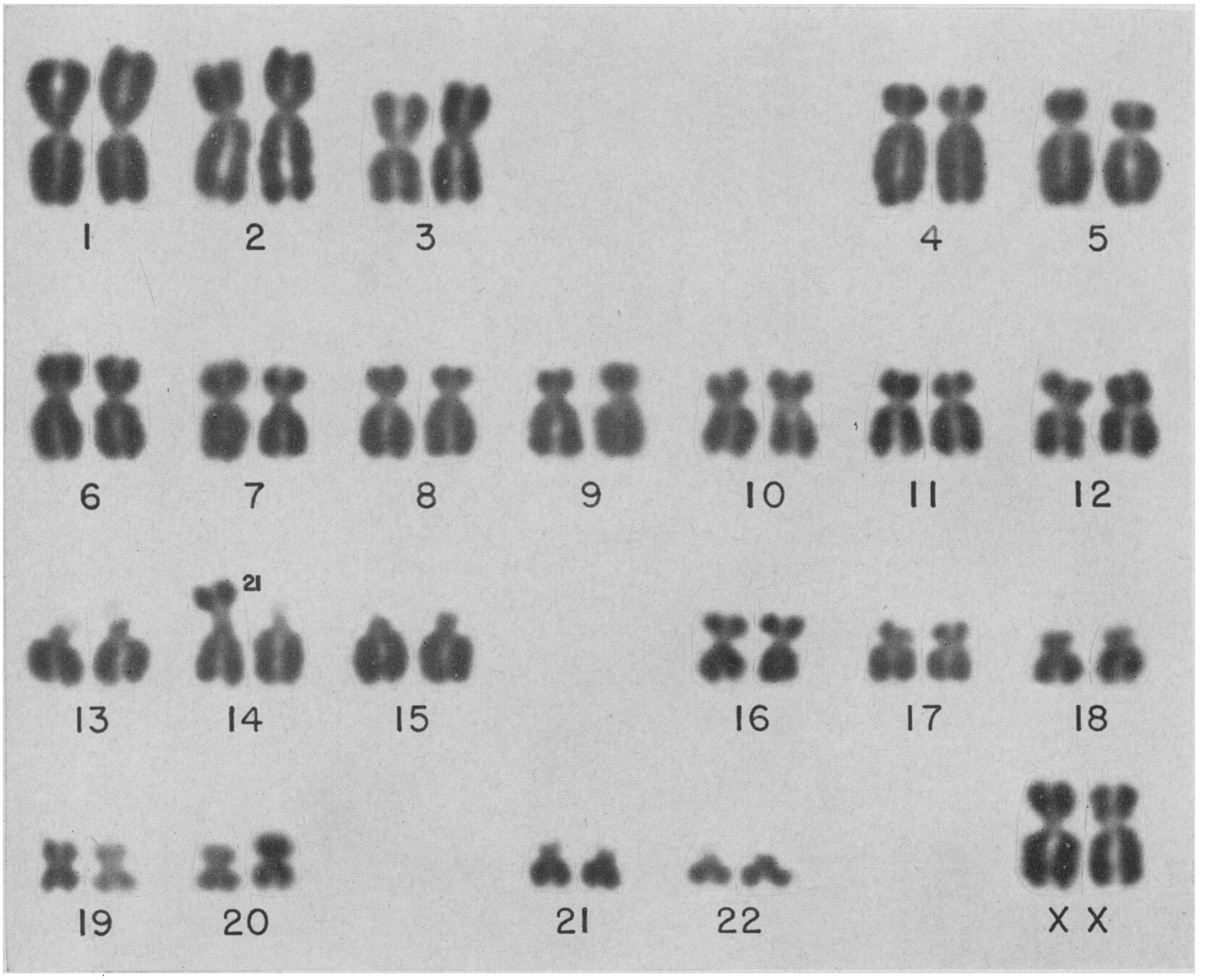

Fig. 2.—Chromosomes of a female mongol with translocation of number 21 on to one of the 13-15 group.

chromosome,[15] but five of these are probably so unbalanced as to be lethal to the developing embryo.[16] The other three genotypes are known to exist from the study of offspring of carrier parents. To reduce this to its simplest terms, let us suppose that the translocation chromosome undergoes normal pairing with the normal (free) member of the 13-15 group, each then separating and entering a different gamete. Then suppose the unpaired chromosome 21 enters either gamete in a random fashion. This gives four alternative gametes (Fig. 4).

Fertilization of gamete A will result in an apparently normal individual, who is however a carrier, like the parent. Gamete B yields a normal chromosome complement on fertilization, while gamete C results in a mongol offspring (Fig. 2). Leaving aside the probable lethal combinations (including D) and assuming the simple behaviour of the chromosomes mentioned above, we find that the incidence of offspring A, B and C would each be one in three. This mathematical probability is only tentative, and many more complete family studies will be required before risk figures for mongolism in such families can be confidently predicted.

The other type of translocation involving two members of the 21-22 group is perhaps less common, though several cases have been reported.[7, 10, 12, 17, 18] Transmission of the translocation chromosome from one parent is known to have occurred in four of these families, although the chromosomes of the parent concerned were not identical in each case. Further details of the chromosomes in the carrier parents are beyond the scope of this report.

We have studied two mongol patients with a translocation involving two members of the 21-22 group, an example of which is shown in Fig. 5. Chromosome studies on the parents of our patients are not yet complete.

CHROMOSOME MOSAICISM IN MONGOLISM

The occurrence of cells with different chromosome numbers in the same organism has long been known to exist in plants, but was first demonstrated in a human with an abnormal sex chromosome complex.[19] Such a mixture of cells with different chromosome complements is known as mosaicism. It was not surprising to find mosaicism also in sub-

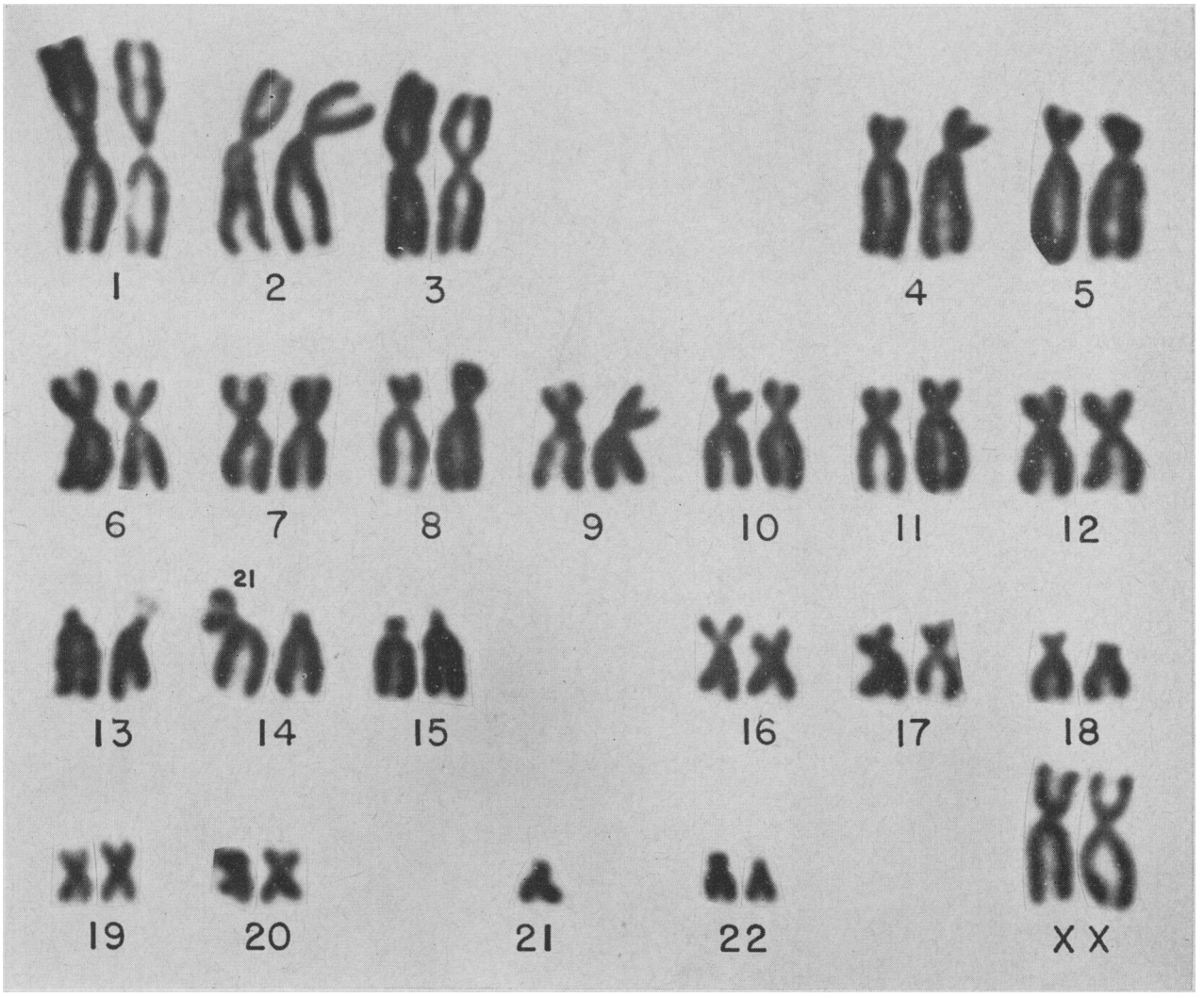

Fig. 3.—Chromosomes of a clinically normal carrier with one of the 21 chromosomes translocated on to one of the 13-15 group.

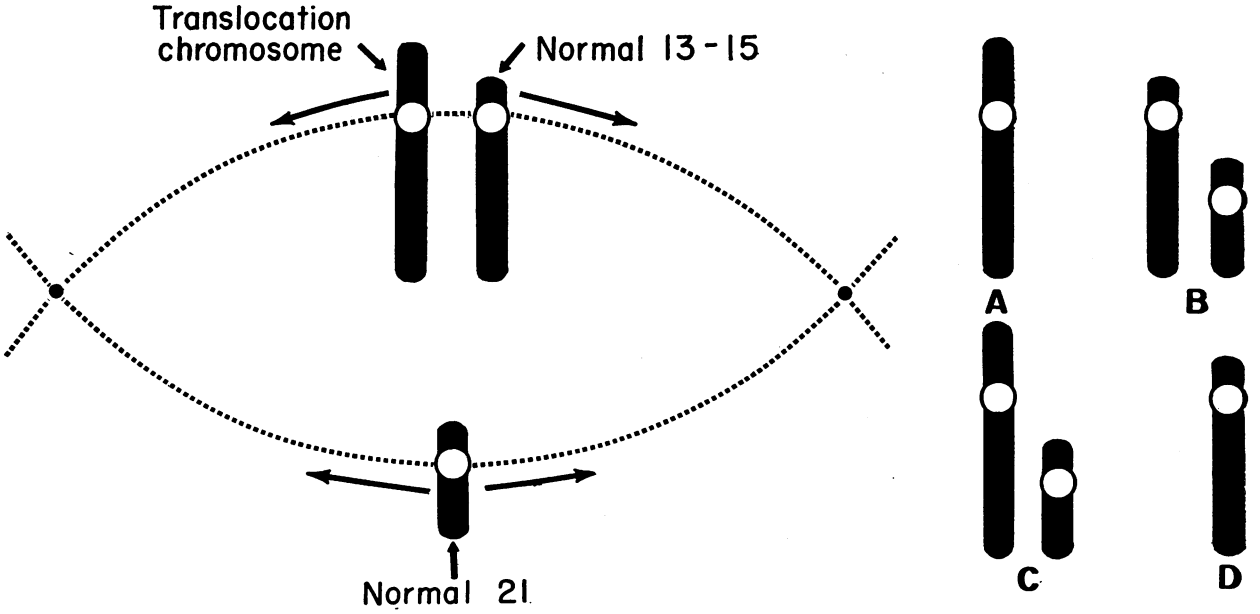

Fig. 4.—Simple explanation of gametes in translocation carriers. Diagrammatic representation of the behaviour of the translocation chromosome, the free member of the 13-15 group and the 21 chromosome during meiosis in the carrier's germ cells.

Canad. Med. Ass. J.
Sept. 1, 1962, vol. 87

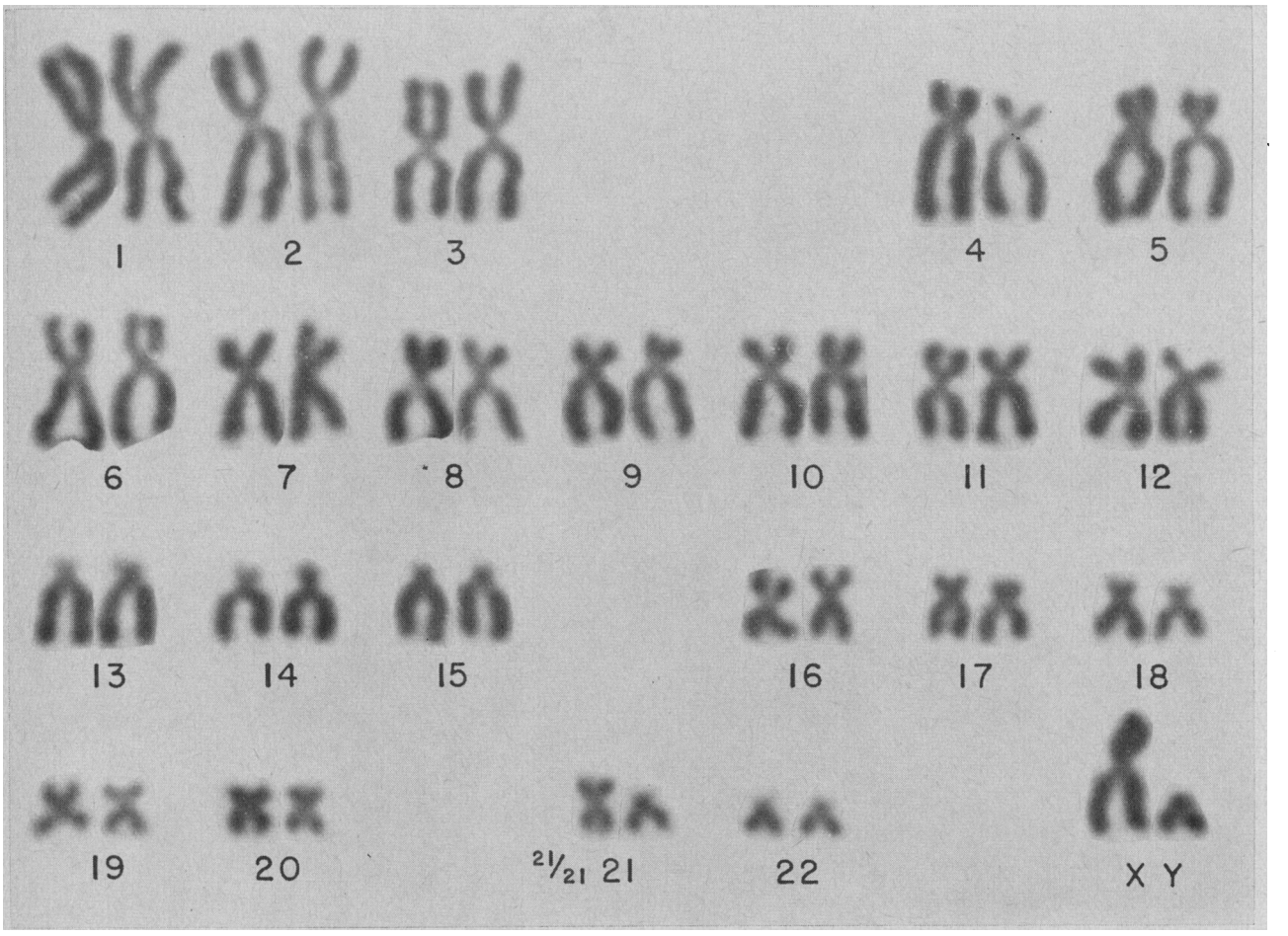

Fig. 5.—Chromosomes of a male mongol with translocation of one chromosome 21 on to another member of the same group (21-22).

jects with abnormalities of the autosomes. Clarke, Edwards and Smallpeice[8] reported the case of a girl who was suspected of being a mongol at birth. Her subsequent development appeared normal, and her I.Q. at 2 years 3 months was 100. However, the palm prints and other features were suggestive of mongolism, and chromosome studies were made. These showed a mixture of normal female cells (44 + XX) and cells containing an extra chromosome 21. Since then several similar cases have been reported, in which the diagnosis of mongolism was in doubt.[20-22] In other cases, chromosome mosaicism has been demonstrated in mongol patients who were clinically typical in every way.[23-25]

The importance of the mosaic is that the diagnosis of mongolism is often not clear-cut, and a definite prognosis regarding future development must be guarded. From the cases already published, we can judge that the ultimate development of a mongol mosaic may range from severe retardation to normal development. This diagnosis may be made with increasing frequency, and as several cases are known to have been seen in other centres it is probably not very rare (see discussion in the report of Nichols *et al.*[26]).

The origin of mosaicism is uncertain, but it probably arises from a trisomic zygote in which one of the extra chromosomes is lost during the first division into two blastomeres.

Yet another possible cause for the incomplete manifestation of mongolism is demonstrated by a case described by Ilbery, Lee and Winn.[27] Here, a boy with some features of mongolism was found to be trisomic for chromosome 21, but one of the three was much smaller than the others. Apparently some of the extra genetic material had been lost, so that the patient had only partial trisomy.

CONCLUSION

When the presence of an extra chromosome was demonstrated in mongolism, it appeared that an infallible method of diagnosis had materialized. This proved to be an oversimplification of the facts. However, chromosome studies in mongolism have assumed considerable clinical importance. Perhaps the most important aspect is the necessity of studying the chromosomes of mongols born to young parents. If studies of the child's cells show trisomy for chromosome 21 and the parents have normal chromosomes, the chances of a second child being born a mongol are 1 or 2% irrespective of maternal age.[28] However, if one of the parents is a carrier of a translocation chromosome, the chances of a second mongol child being born are greatly in-

creased—even as high as one in three. This risk is perhaps less if the father is the carrier.[15, 29]

The incidence of mongolism in cousins,[1] and the occurrence of trisomy in more than one mongol sibling in whom the chromosomes of the parents are normal,[17, 30, 31] suggest an underlying genetic mechanism as a cause of non-disjunction. This is also supported by the occurrence of different types of chromosome abnormality in the same family tree.[31-33] Such a genetic mechanism as a cause of non-disjunction is known to occur in Drosophila.

With the accumulation of larger numbers of complete chromosome studies in the families of mongols, the risk figures for the recurrence of mongolism in a family will be reassessed. They will no doubt be divided into two groups: those with chromosome abnormalities in the parents and those without such visible abnormalities.

The occurrence of mosaicism in mongolism is also of great clinical significance. From our knowledge of the existence of mosaicism, it is clear that a child showing incomplete stigmata of mongolism may in fact have a chance of normal development. It should be stressed, however, that such cases are exceptional; and judging by those already reported, the prognosis for mental development is difficult to assess. The published cases ranged from typical mongols with severe retardation to doubtful mongols with normal mentality. The presence of mosaicism in a baby would necessitate careful observations of the developmental landmarks in the first year before a prognosis could be given.

SUMMARY

Chromosome studies in mongolism have considerable clinical importance. They are mainly valuable in two less common types of cases: mongols born to young mothers and mongols with incomplete manifestations of the syndrome. In the former category, chromosome studies should be extended to parents and siblings if the mongoloid child has the translocation chromosome, in order to provide a basis for genetic counselling. In the case of mongols with incomplete manifestations, chromosome studies may indicate that judgment as to prognosis should be delayed and guided by the child's progress during the first year.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

It is interesting to recall the fact that abdominal surgery is only a little over a hundred years old; because, although various abdominal operations have been performed by heroic surgeons from the earliest times, it was the establishment upon a secure basis of the operation of ovariotomy that secured the proper recognition of abdominal surgery generally. The first successful ovariotomy was one of the triumphs of the New World, for it was performed by Ephraim McDowell, of Kentucky, in the year 1809. Naturally, this historical case did not by itself establish ovariotomy upon a secure basis; on the contrary, for many years there was much opposition and there were few cases. McDowell himself performed the operation only twelve times, with eight recoveries; and for the span of a generation the attitude of the profession was mainly one either of scepticism or of more or less thinly veiled disapproval. The next important advance was made by Charles Clay, of Manchester; his first successful ovariotomy was in 1842, and in all he operated on three hundred and ninety-five patients, with one hundred and one deaths, his mortality being thus about 25 per cent. Think of the courage that must have been required to persevere in the performance and the advocacy of an operation that was attended, at its best, with a mortality of 25 per cent. In 1861, Tyler Smith, speaking from the presidential chair of the Obstetrical Society of London, could utter these pessimistic words, "In the long run, I believe, the results cannot be favourable, either in general or special hospitals." Happily, Tyler Smith's gloomy forecast has not been fulfilled; and by way of illustration and commentary I may mention that at the Chelsea Hospital for Women during the twenty-five years, 1885 to 1910, eight hundred and forty-eight ovariotomies were performed, with forty-seven deaths, giving a mortality of 5.5 per cent.; and if we compare the beginning and the end of this period, we find that in the first five years there were seventy ovariotomies, with nine deaths, or 12.8 per cent.; whilst, in the last five years, there were two hundred and four ovariotomies, with seven deaths, or 3.4 per cent. The results in general hospitals, which at one time were deplorable according to our present standard, are now practically as good as in the special hospitals.—Address in Surgery, by Arthur E. Giles, *Canad. Med. Ass. J.*, 2: 752, 1912.