Chromosomal Aberrations in Man

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FOUR YEARS AGO, the field of human cytogenetics was opened by the demonstration by Tjio and Levan (1956) that the number of chromosomes was 46 in our species. With the increasing efficiency of the methods of tissue culture the karyotype of man began to be carefully analysed and its morphology is now familiar to geneticists.

The study of chromosomal abnormalities is still more recent, for this chapter was opened 22 months ago with the discovery of the mongolian Trisomy (Lejeune, Gautier, and Turpin, 1959a, Lejeune, Turpin and Gautier, 1959b). During these 22 months the number of observations obtained in many laboratories is so vast that at least 23 different aberrations have been collected. At the present rate of about a syndrome a month, the task of a reviewer becomes exceedingly difficult.

To face this challenge the possibility remains of splitting the data into categories so that a new finding can be easily integrated into the proposed plan.

As is usual in experimental genetics, chromosomal abnormalities can be classified in two main types: the aneuploidies, resulting from an abnormal segregation of the chromosomes, and the structural changes, such as deletion, inversion, duplication and translocation.

A. NUMERICAL ABNORMALITIES

It is generally considered that the absence of a given chromosome or its presence in triplicate is related to non-disjunction of paired homologues during meiosis. This postulated mechanism being actually impossible to demonstrate in our species, I plan to avoid the term non-disjunction and to use the more general term "abnormal segregation", which has the main advantage of describing what we know and not implying what we do not know.

In discussing the findings on abnormalities, I shall use the standard system of nomenclature agreed upon in Denver last spring (Report of a Study Group, 1960).

The abnormalities actually known involve both autosomes and sex chromosomes. We will first discuss autosomal aberrations.

1. Numerical aberrations of autosomes

Among the syndromes of mental deficiency, no entity has been more thoroughly investigated and differently explained than mongolism in the course of the 93 years following its description in 1866 by Langdon Down.

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From the clinical data, stereotypy of the features, concordance of monozygotic twins, and reproduction of mongoloid mothers, the indication of a genetic dominant event was obvious, but severely contradicted by the frequency of the condition (a hundred times greater than other known mutation rates).

On the other hand, the existence in mongols and also, to a much lesser extent among their relatives, of minor stigmata which can be inherited in a Mendelian manner in normal people, suggested a polygenic inheritance.

Hence, a dominant event acting on a great number of genes led to the hypothesis of a chromosomal abnormality which was tested in 1958 and established in 1959 (Lejeune, Gautier, and Turpin, 1959b; Lejeune, Turpin, and Gautier, 1959a and b).

That mongolian children are trisomics for chromosome No. 21 can be easily demonstrated. The abnormal count of 47 chromosomes results from an extra small acrocentric, satellited chromosome, not distinguishable from the usual members of pair 21.

Trisomy for 21 explains all the peculiarities of mongolism, even the maternal age effect, but, as we will see later, the number 47 is not obligatorily observed in this condition.

The other trisomics actually described concern clinical entities less well defined than mongolism, for the very reason that in these, individualization has resulted from the chromosomal findings.

One, described by Edwards, Harnden, Camaron, Cross, and Wolf (1960) involves chromosome No. 17, and was found in a girl showing, abnormalities of the skull and of the ears, a webbed neck, and congenital heart disease.

Another, described in two cases by Patau, Smith, Therman, Inhorn, and Wagner (1960), involves one of the big acrocentric chromosomes (group 13–15) and is characterized by cerebral defect, anophthalmia, cleft palate and hare lip, heart disease, etc. The same authors have referred to another syndrome resulting from trisomy of a member of the group 16–18. It is likely that the chromosome involved is the same as in Edwards' patients.

Still another syndrome has been described by de Carli, Nuzzo, Chiarelly, and Poli (1960), in relation to trisomy for a member of the 6–12 group.

Various abnormalities have also been reported in relation to aberrant karyotypes. So, a malformed porencephalic boy was first considered a triploid (69 chromosomes) and secondly as a possible mosaic (Böök and Santesson, 1960a).

Also, by the same authors (in press) a mother and her girl each having an interauricular communication were considered as trisomic for 19 or 20, in part of their cells, the girl being, in addition, monosomic for 21 or 22.

Two cases of Marfan's disease were reported by Tjio, Puck, and Robinson (1959) as presenting a satellite bigger than normal, on 13 for one case and on 21 in the other. Other cases of Marfan's syndrome studied by other workers were considered normal.

2. Numerical aberrations of sex-chromosomes

A few years ago extensive study by endocrinologists of the chromatin body of Barr and Bertran (1949), led to the conclusions that among the gonadal dysgene-

ses, the male type (Klinefelter chromatin positive) had two X-chromosomes, and the female type (Turner, chromatin negative) had only one X. This last point was strongly supported by the study of color-blindness among "Turners" by Polani, Lessof, and Bishop (1956).

As first shown by Jacobs and Strong (1959), the Klinefelter syndrome is characterized by the presence of 47 chromosomes with XXY sex chromosomes. Conversely, as shown by Ford, Jones, Polani, de Almeida, and Briggs (1959), only one X is present in patients with Turner's syndrome with a count of 45 chromosomes.

Recently three other sex constitutions have been described:

A so called super female with 3 X's and 47 chromosomes by Jacobs, Baikie, Court-Brown, MacGregor, MacLean, and Harnden (1959), who is, in fact a hypofemale better defined by the term of 'Triplo X.'

A case of hypofemale having one normal X and another one partially deleted was described by Jacobs, Harnden, Court-Brown, Goldstein, Close, MacGregor, MacLean, and Strong, 1960.

And, finally, a curious constitution (explained only in terms of two abnormal segregations) of 48 chromosomes with XXXY, in two individuals showing both Klinefelter syndrome and primary amentia, by Ferguson-Smith, Johnston, and Handmaker, (1960).

Table 1 shows a summary of the data concerning distributions thus far observed.

The masculinizing action of the Y is evident and it is also obvious that an overdosage of the X chromosome does not much increase the female characteristics and may even decrease them in certain combinations.

Moreover, most of the abnormal combinations reduce the intelligence of the carrier, an old observation in Klinefelter and Turner syndromes, recently confirmed in the Triplo X condition.

For example, among 595 oligophrenic females, three cases were Triplo X as shown by Fraser, Campbell, McGillivray, Boyd, and Lennox (1960).

The preceding conclusion on the masculinizing action of the Y chromosome has to be tempered by two other observations.

First, the syndrome of testicular feminization shows a normal male XY karyotype (Jacobs, Baikie, Court-Brown, Forrest, Roy, Stewart, and Lennox, 1959, and Lejeune, Turpin, and Gautier, 1960), and also some patients with primary

TABLE 1. SEX CHROMOSOME KARYOTYPES THUS FAR REPORTED

Karyotype		Chromatine	Phenotype	
44A	Y	?	unknown	
44A	XY	○	normal male	
44A	XXY	*	sterile male	KLINEFELTER
44A	XXXY	* *	sterile male	KLINEFELTER
44A	X	○	sterile female	TURNER
44A	XX	○	sterile female	
44A	XX	*	normal female	
44A	XXX	* *	normal female (?)	TRIPLO-X

gonadal dysgenesis with a female phenotype can have a male XY formula (Harnden and Stewart, 1959 and Grouchy, Cottin, Lamy, Netter, Netter-Lambert, Trevoux and Delzant, 1960).

Secondly, in true hermaphroditism (Hungerford, Donnelly, Nowell and Beck, 1959; Harnden and Armstrong, 1959; and Lejeune, Turpin, and Gautier 1960) the female constitution XX allows the appearance of a testicle associated with an ovary or at least, the development of an ovotestis. The general morphology of these individuals is more male than female looking.

Hence, exactly as in *Drosophila*, we are aware that the chromosomal constitution (sex chromosome dosage) determines the phenotype, but that some mutant genes can entirely reverse the apparent sex of the carrier.

It is to be noted that in many instances of intersexual syndromes the possibility of mosaics has been raised by various authors; XXY/XX by Ford, Polani, Briggs, and Bishop (1959); XX/X by Ford (1960); XY/XXY by Bergman, Reitalu, Nowakowski, and Lenz (1960); and XX/XXX by Jacobs, Harnden, Court-Brown, Goldstein, Close, MacGregor, MacLean, and Strong, (1960).

The question of human mosaicism which was first raised by Ford, has been and is still the subject of some uncertainties. The fact that two or three types of cells are present in the growth from a single biopsy of bone marrow or even of skin, raises the possibility that the variegation is a continuous one. That is, the mosaicism would be due to an instability of the karyotype not to the imperfections in experimental conditions. The other hypothesis, of a loss or gain of one chromosome during early embryonic development, would probably lead to topographical chimerism in preference to the mixed mosaics observed.

Another point of consideration is the tissue from which the sample is taken, because a chromosomal variegation in blood or in bone marrow would seem much more likely than in ordinary connective tissue.

I do not think that the question of the occurrence of mosaics can be solved at present, because the validity of a bimodal distribution curve of cell types in these cases can not yet be fully tested by statistical analysis of the currently available data.

B. STRUCTURAL ABNORMALITIES

The roughness of our present determination of individual chromosomes does not permit the detection of minor structural changes like:

reciprocal translocations of essentially equal parts
inversions
and small deletions or duplications.

Intrachromosomal inversions are evidently undetectable, and deletions or duplications have to be at least of the order of one per cent of the haploid length to be detectable.

Non-reciprocal translocations are much more evident, especially if they occur between acrocentric chromosomes, a phenomenon generally and incorrectly called centromeric fusion. The fact that the six instances of translocations now published concern this type does not signify that the fusion of acrocentric chromo-

somes is a preponderant accident; the other types would be extremely difficult to assess with certainty. The observed excess of one type of translocation may be more or less related to the present stage of our standards of detection.

The first example of translocation was of Polydysspondylie (Turpin, Lejeune, Lafourcade, and Gautier, 1959). In this boy, with insufficient development of the body and borderline intelligence, multiple lesions of the vertebrae were observed. The karyotype was of 45 chromosomes with the absence of one of the small acrocentrics, probably 22. The abnormal presence of chromatic arms on a 13 chromosome led to the conclusion that 22 had been translocated by centromeric fusion to the 13 chromosome. The condition could be related to a loss of genetic material during the elimination of one of the centromeres.

This example of translocation remained isolated until the discovery by Polani, Briggs, Ford, Clarke, and Berg (1960), of the first abnormal mongol with 46 chromosomes.

The picture of the translocated chromosome, probably 21 $\sim$ 14 was very similar to that reported by Turpin *et al.* (1959), but this girl exhibited also two 21 and two 22 chromosomes. Hence this exception confirmed the rule of trisomy, for the 21 was triplicate, two being free and one being translocated.

The possible implication of this finding in explaining the very rare accumulation of mongolism in certain families was discussed by Lejeune (1960) and demonstrated separately by Penrose, Ellis and Delhanty (1960), on the one hand, and Carter, Hamerton, Polani, Gunalp and Weller (1960) on the other.

In these two families the mongols are of the 46 chromosome type with a 21 $\sim$ (13–15) translocation. The carrier mothers are of the 45 chromosome balanced type due to the translocation which was followed for 3 generations.

The mechanism of production of mongols is obvious in these cases. A mother carrying the translocation can give rise to balanced or unbalanced gametes depending on the fact that the free 21 may migrate or not to the same pole as the translocated one.

Other types of 46 chromosome mongols have been reported; one resulting from a 21–21 translocation (Fraccaro, Kaijser and Lindsten, 1960) possibly transmitted through the father; another resulting probably from a 21–22 translocation (Penrose, Ellis, Delhanty, 1960). Another type of translocation probably involving a part of the Y and of the 21 was found by Lejeune, Turpin, and Gautier (1960) in a pseudo-hermaphrodite child with dextrocardia.

C. COMPLEX ABNORMALITY

Two instances of double abnormalities have been reported.

One is related to a mongol exhibiting also the Klinefelter syndrome (Ford, Miller, Mittwoch, Penrose, Ridler and Shapiro, 1959) and showing both the XXY and 21 trisomy abnormalities.

The other concerned an apparently typical Klinefelter (Lejeune, Turpin, and Decourt, 1960) having the classical XXY type but showing only 46 chromosomes due to a translocation between chromosomes 14 and 15 resulting in a new big metacentric chromosome.

These observations are worthy of two remarks:

First, the accumulation of abnormalities in the same gamete can be greater than expected by chance alone;

Secondly, a first abnormality can be the cause of a second as, for example, in Drosophila, some autosomal inversions increase the probability of abnormal segregation of the X.

SUMMARY

This extremely brief survey of the present stage of cytogenetics gives us some indication of the future possible developments of this new field of human pathology.

Three main goals are in view, but nobody can presently foresee when they will be reached.

First, the desire of human geneticists to map the chromosomes of our species has been greatly enhanced by these new results. Unfortunately, the cytological map of human chromosomes is still remote; mainly because of the impossibility of detecting stable and recognizable structures in the chromosomes themselves; something like the banding pattern of the polytenic chromosomes of the salivary glands of diptaera. We have evidence in our laboratory that a structural differentiation can occur in human chromosomes in tissue cultures, but the conditions of production of this phenomenon are entirely unknown. These artificially produced chromomeres might, if readily reproducible, have a tremendous impact on the rate of discovery of chromosomal rearrangements.

Another use of chromosome studies was opened by Bender in 1958, in assessing the damages produced by X-raying human tissue cultures. Other work in this area is in progress in many laboratories (Tjio and Puck, Chu, and Fraccaro), and important results concerning the high sensitivity of human chromosomes to ionizing radiation have been obtained.

It would be useful to test directly in the progeny of irradiated individuals if the frequency of abnormal segregation of chromosomes is increased by radiation exposure. A research program on this subject is now in progress in Paris to check if these accidents play a role in the decrease of the sex ratio in the progeny of irradiated mothers (Lejeune, 1959a).

This use of chromosomal aberrations in radiation research is, so to speak, a by-product of the recent improvements of the techniques, and the last goal is to relate the chromosomal changes observed under the microscope to biochemical changes occurring in the cells or even in entire individuals. The available data on the biochemical defects of Turner or of Klinefelter patients are too scanty to form a picture of the genic content of the X, except for some sex-linked genes previously known, such as color blindness. Research in this field is particularly needed.

In the case of the mongolian trisomy, some observations have been made in our laboratory (Jérôme, Lejeune, and Turpin, 1960) which could possibly throw some light on the gene content of chromosome 21.

Without going into too much biochemical detail it can be briefly stated, that

before or after tryptophan loading, the mongolians differ from the normals by a low excretion of 5-hydroxy-indoleacetic acid, indol acetic acid, and xanthuneric acid; the excretion of kynurenine showed no significant change in the investigations.

Those observations, consistantly made on 15 mongols and 16 controls, lead to the hypothesis that mongols suffer from a disturbance of the tryptophan metabolism and, curiously enough, are probably affected by a low serotonin content of the brain, like phenylketonurics (Pare, Sandler, and Stacey, 1957).

The mechanism actually envisaged to explain these data is an acceleration of the normal pathway through kynurenine and 3 OH-kynurenine toward products of the type of anthranilic acid and others.

If this metabolic hypothesis is confirmed, the action of the trisomy could be explained in the following way: the genic overdosage produces an over concentration of specific enzymes (here, those concerned in the kynurenine pathway); so, there is an acceleration of some normal reactions, and conversely a deprivation of other chains, due to the exaggerated turnover in one direction.

Evidently these views, at present purely theoretical, would lead to various conclusions—first, the localization on the 21 chromosome of some genes controlling the production of the enzymes involved, secondly, a possibility of chemical correction of the defect.

It is entirely possible that considering the probably large number of genes located in chromosome 21, the biochemical features discussed above are only a part of the effect of the mongolian trisomy, but they give us a first indication that a link between biochemistry and human cytogenetics is possible even in the very early stage of our present knowledge.

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