MEDICAL INTELLIGENCE

CURRENT CONCEPTS IN GENETICS

Autosomal Chromosome Disorders and Variations

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CHROMOSOMAL abnormalities or variations are related to genetics in three ways: they involve the genetic material, and in that sense are always "genetic"; most of the variants and a proportion of the structural rearrangements are directly transmitted from parent to offspring (i.e., such changes can be inherited); and some of the chromosome abnormalities arise as a result of an aberration in the meiotic process by which the diploid (2n) number of chromosomes is reduced to the haploid (n) number found in sperm and egg. Thus, the common numerical changes (e.g., trisomy 21, 18 or 13) are thought to arise by failure of meiotic separation of a homologous pair of chromosomes (nondisjunction), leading to an ovum or sperm containing 24 chromosomes rather than the usual 23. A meiotic error is also the usual cause of chromosomal imbalance associated with major structural changes.

How to Interpret Changes

The introduction of chromosome-banding technics has made the interpretation of changes easier and far more reliable. Quinacrine (Q-), Giemsa (G-) and Reverse (R-) banding methods provide detailed information about the pattern of bands along each chromosome, and a growing number of special methods provide information about specific bands rich in repetitious nucleotide sequences that are genetically inert, called heterochromatin. With these methods, it is now possible to identify every chromosome and to detect tiny changes that were hitherto undetectable. Trisomy for virtually any chromosome can be readily identified because of the characteristic banding patterns of each chromosome. This identification is important because not every karyotype in which there are 47 chromosomes is a simple trisomy; some, called tertiary trisomies, are produced by 3:1 segregation of chromosomes during meiosis in a translocation heterozygote, or carrier. Although these are less common than simple trisomies, their occurrence is an indication that the parents of the person affected may be at high risk of having other chromosomally unbalanced and abnormal children. It is therefore wise, in questionable cases, to determine the banding karyotype on the presumptively trisomic person and on the parents. Studies in such families have led to the identification of families at high risk of having chromosomally unbalanced children and to the recognition of several partial trisomy syndromes (e.g., trisomy 9p). Experience with such families has convinced us that karyotype analysis should never be performed with nonbanding methods: there are too many possibilities for misdiagnosis and failure to detect the high-risk families to justify reliance on the classic staining methods, even though they can detect numerical changes (e.g., trisomy, mosaicism) and could thus provide a screening test for, say, prenatal diagnosis in older women. Banding methods are just as quick and provide so much more information that their use has already become standard practice in many laboratories.

Structural changes are of two types: major and minor. The major changes are thought to involve breakage of one or more chromosomes and rejoining of the broken ends to give rise to inversion or deletion of a segment of a single chromosome or translocation of material from one chromosome to another (or reciprocally between chromosomes, as indicated in Figure 1). The minor changes involve differences in the size of certain bands that are known to contain heterochromatin. Since this material appears to be genetically inert (that is, is not transcribed to produce messenger RNA), there is no reason to expect that gains or losses would have any effect on the phenotype, and, in general, this lack of effect is borne out. However, it has been reported that an excess of heterochromatin can be associated with detrimental effects. Although their conclusions are not proved, these reports indicate that further study is needed before adequate interpretation of the implications of some of these minor variants is possible.

Major structural changes can occur in either a balanced or an unbalanced form. In the former, there is no apparent gain or loss of genetic material — only a rearrangement of it. One should remember, however, that such chromosomes have undergone one or more breaks, which may have irreparably damaged a single gene if it was the site of breakage. Also, rejoining may have modified the chemical neighborhood of a gene near the breakpoint in such a way that it can no longer function properly. In short, structural rearrangements could damage the genetic material even though the complement appears balanced. Evidence for this hypothesis comes from the observation, summarized by P.A. Jacobs, that approximately one third of the carriers of de novo (as opposed to inherited) balanced translocations are mentally retarded or have other abnormalities.

The unbalanced form of a structural rearrangement occurs as a result of an error in the meiotic separation of the chromosomes in the gonads of a person (who is usually normal) with the balanced form of the translocation or inversion. About 15 per cent of the progeny of a carrier mother have an unbalanced karyotype, and no more than half that proportion when the father is the carrier. Duplications (partial trisomies) and deficiencies (deletions) are the best

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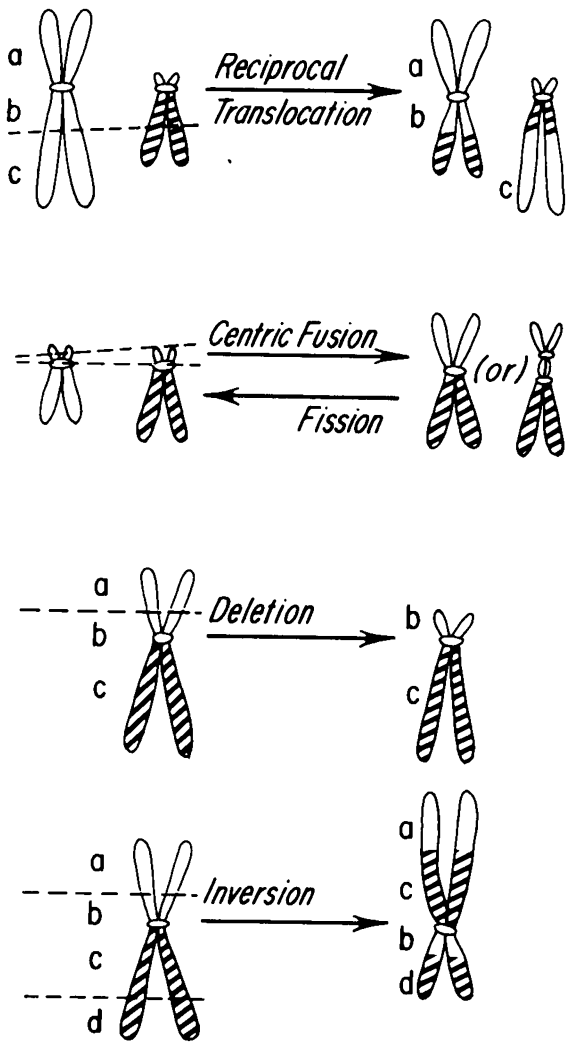

Figure 1. Major Structural Changes in Chromosomes (Dotted Lines Indicate Points of Breakage).

known results. In about one sixth of the cases the 5p- or cat-cry syndrome occurs as a result of such a meiotic error in a parent with a balanced translocation. A comparable proportion of the other well known deletions, 4p-, 13q-, 18p- and 18q-, may arise in the same way. In addition, duplication of specific chromosome segments (e.g., 9p, which has been recognized only since the introduction of chromosome banding) usually arises in the same manner. Most of the clinically noteworthy autosomal abnormalities seen in newborn or older persons are listed in Table 1.

The clinically important structural changes in chromosomes appear to be the result of chromosome breakage. For this reason the physician must be concerned about the protection of every patient, and especially their gonads, from unnecessary exposure to ionizing radiation, radiomimetic alkylating agents, mitomycin or other drugs known to produce chromosome breaks. Certain genotypes are prone to chromosome breakage. The best known are the homozygous patients with Bloom's syndrome, Fanconi's pancytopenia, or ataxia telangiectasia. The much more numerous heterozygotes also appear to have an increased tendency to

Table 1. Clinically Important Chromosomal Abnormalities.*

Trisomy: 21, 18, 13, 8, 22, 9, mosaicism for trisomic & normal cells
Partial trisomy (duplication†): 21q, 13q, 9p, 4p, 10q, 11q, 7q, 14q, 1q, 3p, 4q, 8q, 10p, 11p, 15q, 20p
Monosomy: 21, 22
Deletion of part of (deficiency†): 5p, 13q, 4p, 18p, 18q, 11q, 7p, 9p, 12p
Duplication-deficiency: 3, 4, 2
Triploidy
Chromosome breakage: Fanconi's anemia, Bloom's syndrome, ataxia telangiectasia, glutathione reductase deficiency

*In each category, abnormalities are listed approximately in order of decreasing frequency.

†Some duplications & deficiencies are really combined duplication deficiencies in which 1 or the other chromosomal imbalance predominates.

chromosome breakage. It is possible that such mutant genes, affecting either DNA repair processes or resistance to virus infection, are major endogenous causal factors in the chromosome breakage involved in structural changes.

When to Suspect Abnormality

Certain people are much more likely than others to have a chromosome abnormality (Table 2). Cancer cells frequently show such a change, although the noncancerous cell in the person in whom they occur has a normal karyotype. Evidence is growing that specific chromosome changes occur in association with several kinds of neoplasia, and in chronic myelogenous leukemia, these changes are of diagnostic and prognostic value. More generally, chromosome abnormalities are present in all the cells and tissues of the body, although cases of chromosomal mosaicism (mixoploidy) exist in which a person has two or more cell lines with different chromosome constitutions. The presence of an unbalanced complement of genetic material interferes with normal cellular differentiation and function, and this effect tends to lead to lethality, to malformations, to physical and mental retardation, or to other poorly understood disorders of the central nervous system, manifested by infantile autism, childhood schizophrenia, or seizure disorders.

What to Do about Chromosome Changes

Chromosome studies are done to establish a diagnosis in clinically affected persons, to assess recurrence risks in families, and to monitor high-risk pregnancies in families in which abortion is acceptable. Nothing can be done to alter the chromosome constitution of a person. Cells in culture are able, under certain conditions, to ingest whole chromosomes and to incorporate an essential gene while getting rid of most of the chromosome, but this kind of genetic engineering is not possible with human beings, whose cells ap-

Table 2. Approximate Frequency of Chromosome Abnormality in Some Groups.

Group	Frequency (%)
Chronic myelogenous leukemia	80-85
Spontaneous abortuses	40-60
Multiple malformations, with mental retardation	10-15
Intrauterine growth retardation	4-6
Stillbirth & early neonatal death	4-6
Infertile males	2-3
Mental retardation	2-3
Live birth	0.5

pear to have no way of correcting or adjusting to an unbalanced chromosome complement. What one can do after diagnosing such a condition depends on the time of diagnosis. If the diagnosis is made early enough in pregnancy, termination of the pregnancy will prevent the birth of an affected child. This procedure has found wide acceptance in chromosome changes that produce a severely affected and inadequately treatable condition such as Down's syndrome. It may not be so acceptable when one is dealing with less severe chromosomal abnormalities.

When prevention is not the answer, what can be done? The answer will depend upon the nature of the chromosome change and the type of abnormality expected with it. If it is 13q-, one should be on the lookout for the development of retinoblastoma. In some cases one will be able to provide the parents with a fairly comprehensive prognosis based on previous experience with the better known karyotypic changes. In many cases, however, information is still too limited to do more than alert the family and the physician to the possibility of unexpected malformations, seizures, psychomotor retardation or behavioral problems, facilitating early diagnosis and management.

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DISSEMINATED GONOCOCCAL INFECTION AND TENOSYNOVITIS FROM AN ASYMPTOMATICALLY INFECTED INTRAUTERINE CONTRACEPTIVE DEVICE

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DISSEMINATED gonococcal infection has been increasingly recognized as a cause of acute septic arthritis and tenosynovitis.[1-4] However, despite recent improvements in culture technics, which have allowed more frequent isolation of *Neisseria gonorrhoeae,* suspected cases remain undiagnosed. In the following case an intrauterine contraceptive device, previously unrecognized as a source of asymptomatic infection, produced disseminated gonococcal infection.

Case Report

In a 36-year-old nurse fever (temperature of 39.8°C) and chills developed, followed by severe pain, swelling and redness in the left hand, with restricted extension of her third, fourth, and fifth fingers. After the onset of a skin rash, accompanied by arthralgia of both ankles and elbows, she was admitted to the hospital. Symptoms had begun two days after completion of her menstrual cycle. On admission the temperature was 37.2°C. There was marked tenosynovitis involving the third through fifth extensor tendons on the left hand, with one area of fluctuance. Tenosynovitis of the left tibialis anterior was also present. Five erythematous skin lesions with necrotic centers were on the hands. Pelvic examination was completely normal. A Dalkon Shield intrauterine device was in place. The fluctuant area was aspirated and cultured on Thayer–Martin medium, as were swabs of the cervix, rectum, and throat. Blood cultures were obtained. The hematocrit was 42 per cent. The white-cell count was 11,900 with a normal differential. The sedimentation rate was 62 mm per hour (Westergren method). Urinalysis, liver, and muscle enzymes, serum protein electrophoresis, total hemolytic complement (CH_{50}), C_3, C_4, were within normal limits. An L.E. preparation and test for antinuclear antibody were negative. Latex fixation was positive at a dilution of 1:1280.

All initial cultures (cervix, rectum, throat, subcutaneous aspirate) were negative. A second pelvic examination was performed. After the intrauterine device was removed and plated on Thayer–Martin medium, cultures were again obtained from these sites. Both the device and repeat cervical cultures grew *N. gonorrhoeae.*

Because of known penicillin allergy, the patient was treated with erythromycin. The tenosynovitis improved rapidly, disappearing after three days. Five months later she remained asymptomatic, and the latex-fixation titer had returned to normal levels.

Discussion

Fever, chills, typical skin lesions, arthralgias and tenosynovitis were strongly suggestive of disseminated gonococcal infection. This presumptive diagnosis prompted culture of the intrauterine device with isolation of *N. gonorrhoeae.* Disseminated gonococcal infection is estimated to occur in 0.1 to 1 per cent of the infected female population.[1-3] However, many suspected cases have negative cultures: Holmes[1] and Keiser[3] described nine and 11 patients, respectively, from whom no positive cultures were obtained, but whose clinical courses were indistinguishable from disseminated gonococcal infection. The number of wearers of intrauterine devices was not provided. In the future, such devices must be considered a possible source for disseminated gonococcal infection.

The mechanisms by which an intrauterine device produces an asymptomatic infection with subsequent dissemination are not known.[5-7] Mishell and Moyer[7] found the uterine cavity sterile at 48 hours and 30 days after insertion of such a device. Recent evidence suggests a ninefold increase in first-episode acute pelvic inflammatory disease in wearers of intrauterine devices.[5,6]

Tatum et al.[8] compared bacteriologic cultures from tails of the controversial Dalkon Shield, Cooper T and Lippes Loop. Positive anaerobic or aerobic cultures were obtained only from the Dalkon Shield. The authors suggested that the multifilamentous structure of the Dalkon-Shield tail facilitated the passage of organisms into the uterine cavity.[8]

Within the uterus, local defense mechanisms are important in preventing further infection. The intrauterine device, a foreign body, invokes a cell-mediated, immune response in the adjacent endometrium[9]; macrophages migrate and adhere to the device.[10] Myatt[11] cultured macrophages from devices removed from normal patients and demonstrated release of appreciable amounts of prostaglandins E_1 and F_2 alpha. Polymorphonuclear cells release prostaglandin E_1 during phagocytosis.[12] Since prostaglandin E_1 may delay the fusion of lysosomes with phagocytic

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