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II. GENERAL CONSIDERATIONS

A. Fundamental aspects of human epidemiology

Aetiologies of congenital malformations

The development of the embryo is the resultant of two factors: the genetic information, which contains the programmation of the whole phenotype of the future child, and the environment, which supplies the nutrients necessary for growth and differentiation of the embryo.

Hence, congenital malformations may be determined in four ways (Fig. 1).

– *Genetic malformations:* a defect in a genetic factor is produced at the origin by a mutation and transmitted hereditarily. The defective gene is expressed immediately in the phenotype if it is dominant, but remains hidden until a homozygous conditions comes about if it is recessive.

– *The chromosomal aberrations:* represent a gross imbalance in a genome and result in important and complex malformations though the individual genes are normal. For instance: trisomy 21 in which the presence of three 21-chromosomes instead of two induces the Down syndrome.

– *Exogenous malformation:* The genome is normal and well balanced but its expression is impaired by exogenous factors present in the environment and acting in the course of the embryonic development and having a teratogenous effect.

– *Multifactorial malformations:* No clear-cut genetic defect exists but the expression of one gene or several genes is modified by small doses of a teratogen which are harmless for the progeny of the most part of the population. In this case, the expression of the gene concerned is at the limit of the normal and a slight impairment caused by exogenous actions brings it below a threshold separating the normal phenotypic trait from the malformation. This instability in the expression of some genes is at the origin of most of the usual congenital malformations.

In man, recent investigations have shown that the proportion of pregnancies ending in foetal or neonatal deaths is approximately 25%. Among the living newborns the incidence of malformations has been estimated to be 3% to 5%. One fifth of these (1%) are assumed to originate from a genetic defect. The chromosomal aberrations represent about 0.5% and the great majority is represented by the exogenous and multifactorial malformations.

B. Genetic malformations

The nucleus of the fertilized egg contains two sets of genetic information: the paternal one and the maternal one. All this information is transmitted to every cell in the embryo. The first step in the differentiation of an organ consists in a selective "derepression" of a particular series of genes which characterize the specific activity of the differentiated cell. This selective

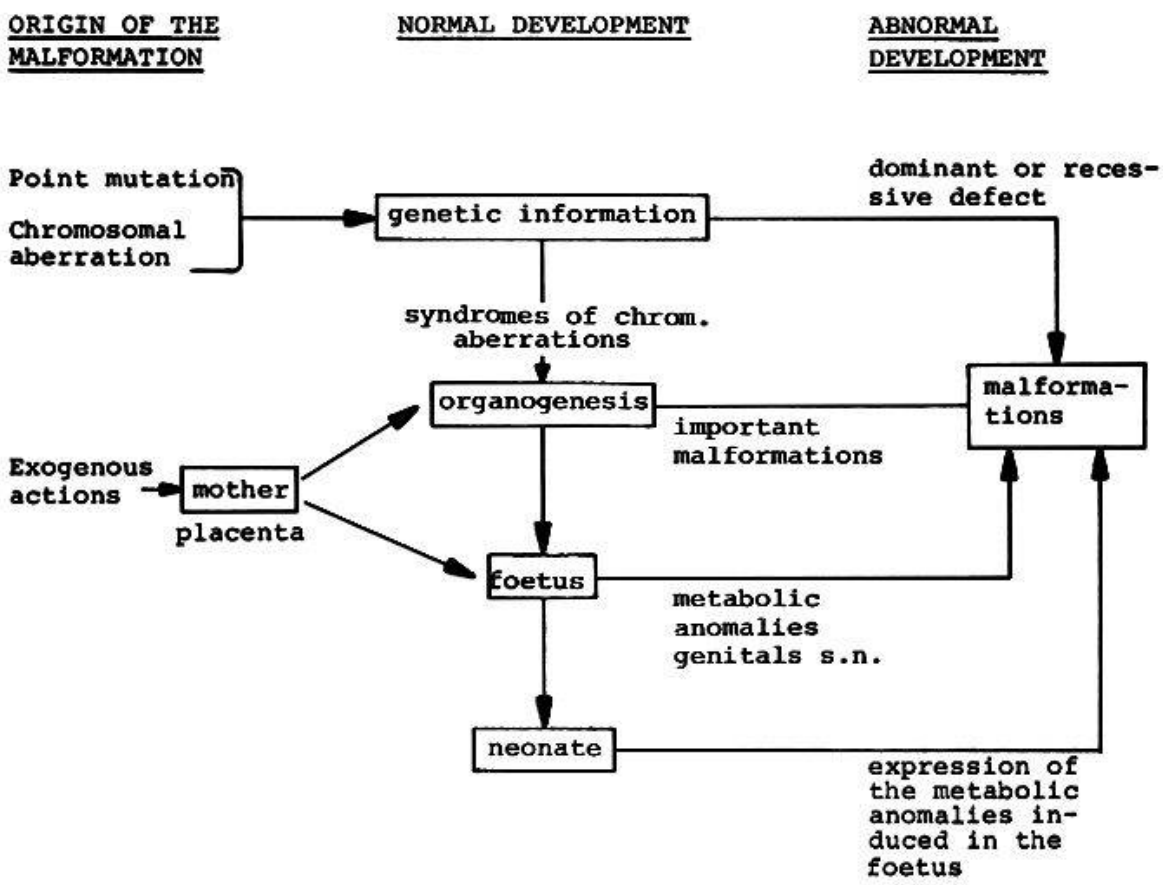

Fig. 1. Aetiology of the congenital malformations.

expression is controlled by the micro-environment represented by the cells of the neighbouring tissues. If a mutation exists in the active genes of the differentiating cell or of the controlling tissues, the normal development of the organ is impaired and a malformation may occur.

1. Spontaneous mutations

A number of agents are known to produce mutations, but many mutations appear without any recognizable cause. They are errors inherent in the replication process of the DNA molecules in which the genetic information is coded. The genetic defects described in man so far, both dominant and recessive, have been reported by McKusick (1971).

A mutation producing a dominant defect is immediately recognized: when a child bearing this defect is born of normal parents, it is concluded that the defect must have arisen through a genic mutation. In fact, the expression of a dominant gene may be more or less inhibited by other genes having a modifying effect on it. This influence of the genetic background explains the phenomenon of the "skipped" generation, in which an apparently normal child has received from his father a dominant noxious gene, which is not expressed in him (low penetrance of the gene), but may express itself fully in his son.

A mutation producing a recessive defect cannot be recognized as soon as it occurs: the heterozygous child bearing a recessive mutant gene is phenotypically normal; the new gene is transmitted and remains dormant in the population as long as a homozygous condition does not come about.

It is possible to calculate the general frequency of these affected genes in the general population from the incidence of affected individuals (HARDY-WEINBERG law)[1]. Calculations, made by very indirect approaches, indicate that each human individual bears in his genome three to eight recessive unfavourable genes. VOGEL (1970) arrived at an estimate of about 17.5 mutations/germ cell generation. This would mean that every individual carried an average of about 35 mutations which had originated in the germ cells of his parents. This "genetic load" could become still heavier in the future by the progress of therapeutics enabling abnormal individuals to survive and to reproduce, i.e. individuals who otherwise would have been eliminated through "natural selection".

An equilibrium is established between the mutation rate and the simultaneous loss of these mutated genes by poor fertility or death of the affected subjects. But this equilibrium is shifted when the heterozygous conditions confer a selective advantage or an increased fertility by comparison with the normal homozygotes. For instance, individuals who are heterozygous for sickle-cell anaemia have increased resistance to malaria compared to the rest of the population, which confers on them a selective advantage. While the proportion of sickle-cell anaemia genes in the population of countries with endemic malaria is abnormally high, it decreases slowly in the course of the following generations, when malaria is eradicated. This well-known example of heterozygous fitness is not unique and such a "balanced polymorphic system" may exist for a number of recessive conditions like phenylketonuria, mucoviscidosis and Tay-Sachs disease.

The mutations should theoretically occur randomly at any locus, but, in fact, the mutation rates differ for different loci and must be determined for each of them.

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[1] *The Hardy-Weinberg law:* Let us consider a pair of allelic genes in a population, where the frequency of the one gene is p and that of the other is q, the total sum being therefore $p+q=1$ (= 100%). If there is random mating (panmixis) in the population, the genotypes arising from the various gametic combinations will be represented in the next generation in the following frequencies:

$(p+q)^2=p^2+2pq+q^2$

where p^2 is the frequency of the normal individuals ("normal homozygotes"),

$2pq$ that of the heterozygotes ("carriers"), and q^2 that of the "affected homozygotes".

The relative proportions $p^2:2pq:q^2$ will remain the same also in the following generations, provided that there are no changes in the structure of the population.

Based on the proportion of the various genotypes, it is possible to calculate each of them, if we know the frequency of the manifestation (q^2) in the population.

2. *Determination of the mutation rate*

The mutation rate is *the number of modified genes per locus per generation.* It is often expressed as the number of modified genes per given number of gametes at each generation.

Two methods are used for its determination:

The *direct method,* which can only be used for dominant affections with complete penetrance. It consists in counting the number of affected children born of normal parents (n = "sporadic cases") and putting it in relation to that of the total number of births (N). The algebraic formula for the mutation rate (μ) is:

$$\mu = \frac{n}{2N}$$

The double number of born children (2N) in this formula is due to the fact that the mutation rate is not based on the number of individuals, but on that of the genes of the concerned locus.

Errors may arise from fluctuations in the penetrance of such genes and the existence of phenocopies induced by exogenous agents which are taken for mutations.

The *indirect method* is based on the assumption of equilibrium between new mutations and gene elimination by natural selection. It takes into account the frequency of the affected subjects in the population and their relative fertility. Thus, the quantitative determination of the gene loss by reduced fertility in every generation permits at the same time the evaluation of the mutation rate.

The value of both the direct and indirect methods depends to a large extent on the possibility of investigating a sufficiently large and representative population in order to ascertain all the bearers of a specific genetic trait. Other sources of error inherent in both methods may be heterogeneity of phenotypically similar affections as well as fluctuations in penetrance and expressivity.

In particular, as far as the indirect method is concerned, the postulated genetic equilibrium between new mutations and negative selection seems to be specially *questionable for autosomal recessive conditions.* Indeed, the elimination of disadvantageous genes may be partially or wholly offset by the selective advantage of the heterozygote with regard to certain diseases, so that the calculated mutation rate is higher than the real one.

The formulae for calculating the mutation rate are the following according to the different modes of inheritance (see Table 1).

Mutation rate in relation to paternal age

A number of mutations seem to occur preferentially in male germ cells and the age of the father has been demonstrated to be a decisive factor.

Table 1

Determination of the mutation rate according to the indirect method

autosomal dominant inheritance	$\mu = \frac{1}{2}(1-f)\,x$
autosomal recessive inheritance	$\mu = (1-f)\,x$
sex-linked recessive inheritance	$\mu = \frac{1}{3}(1-f)\,x'$
sex-linked dominant inheritance	$\mu = \frac{2}{3}(1-f)\,x$

$$\mu = \text{mutation rate} = \frac{\text{number of new mutants}}{\text{total number of alleles of a given locus in a population}}$$

f = relative fertility of the affected individual, when the average in the population f = 1

$$x = \frac{\text{total number of affected individuals}}{\text{total population (males + females)}}$$

$$x' = \frac{\text{number of affected males}}{\text{total male population}}$$

Regarding the incidence of achondroplasia, for instance, the age of the father was equal to or greater than 35. Similar correlations seem to exist also for acrocephalosyndactyly Apert and myositis ossificans.

Geographical "isolates"

The multiplication and expression of noxious genes are favoured by consanguineous unions occurring in geographical "isolates" where exceptional hereditary defects may be observed with an unusually high frequency and in a wide range of phenotypical variability. The "opening" of these isolates leads to a dilution of these gene-pools and lowers considerably the incidence of the recessive manifestations.

The following table (Table 2) lists the mutation rates in man according to VOGEL (1970). (The frequencies were taken only from investigations where the size of the material and the methodology of examinations were judged satisfactory). It appears from this table that all mutation rates may range from 10^{-4} to 10^{-6} fertilized gametes per generation. Therefore it must be assumed that these figures represent the general order of magnitude of the mutation rates in man. It is interesting to note that these estimates closely correspond to the figures for spontaneous mutations in mice reported by RUSSELL and SAYLORS (1961) (7.5×10^{-6}) and by SCHLAGER and DICKIE (1966) (2.7×10^{-6}).

Table 2

Selected mutation rates for human genes (F. VOGEL, 1964, 1970)

No	Affection	Population examined	Mutation	Number of mutants/ 1 million gametes
a)	Dominant mutations: More than one estimate			
1	Achondroplasia	Denmark	$1x10^{-5}$	10
		Northern Ireland	$1.3x10^{-5}$	13
2	Aniridia	Denmark	$2.9(-5)x10^{-6}$	2.9(-5)
		Michigan (USA)	$2.6x10^{-6}$	2.6
3	Dystrophia myotonica	Northern Ireland	$8x10^{-6}$	8
		Switzerland	$1.6x10^{-5}$	16
4	Retinoblastoma	England	$6-7x10^{-6}$	6-7
		Michigan (USA), Switzerland, Germany, Japan	$8x10^{-6}$	8
	One estimate only			
5	Neurofibromatosis	Michigan (USA)	$1x10^{-4}$	100
6	Polyposis intestini	Michigan (USA)	$1.3x10^{-5}$	10-30
7	Marfan's syndrome	Northern Ireland	$4.2-5.8x10^{-6}$	4.2-5.8
8	Polycystic disease of the kidney	Denmark	$6.5-12x10^{-5}$	65-120
9	Acrocephalo-syndactyly	England	$3x10^{-6}$	3
10	Osteogenesis imperfecta	Sweden	$0.7-1.3x10^{-5}$	7-13
11	Diaphyseal aclasis (multiple exostosis)	Germany (Reg.-Bez. Münster)	$6.3-9.1x10^{-6}$	6.3-9.1
b)	Sex-linked recessive mutations:			
12	Haemophilia	Denmark	$3.2x10^{-5}$	52
		Switzerland	$2.2x10^{-5}$	22
	Haemophilia A	Germany	$5.7x10^{-5}$	57
	Haemophilia B	Hamburg	$3x10^{-6}$	3
	Haemophilia A	Finland	$3.2x10^{-5}$	32
	Haemophilia B		$2x10^{-6}$	2
13	Duchenne type muscular dystrophy	Utah (USA)	$9.5x10^{-5}$	95
		Northern Ireland	$6.0x10^{-5}$	60
		England	$4.3x10^{-5}$	43
		Germany (Südbaden)	$4.8x10^{-5}$	48
		Wisconsin (USA)	$9.2x10^{-5}$	92
		Leeds (England)	$5.1x10^{-5}$	51

C. Chromosomal aberrations

They are true mutations. Classification in the truly genetic sense is as follows:

Aberrations of the genome: Polyploidy
Aneuploidy Monosomy
Trisomy
Polysomy

Aberrations of the chromosome: Aneusomy

i.e. Deletion	Inversion
Deficiency	Isochromosome
Dicentric chromosome	Ring chromosome
Duplication	Transposition
Insertion	Translocation centric fusion reciprocal

The following classification is used in clinical genetics:

- Autosomal aberration: Numerical or/and structural
- Gonosomal aberrations: Numerical or/and structural
- Mosaicism

Gene mutations are distinct errors of the molecular structure of the genes in the Ångstroem range, whereas chromosomal aberrations concern the morphological structure of the chromatids in the micrometer range, which can be diagnosed by special laboratory techniques under the light microscope. Special techniques of chromosome preparation are used to differentiate circumscribed parts in each chromosome.

Chromosomal aberrations originate *before* conception in the course of meiosis and spermatogenesis, *during* conception in the second stage of meiosis in oögenesis, or *after* conception in mitosis of early cleavage stages leading to mosaicism.

The estimates of frequencies and their importance regarding the aetiology of congenital malformations originate from two main sources:

- Cytogenetic investigations of spontaneous abortions
- Cytogenetic studies in series of newborns

According to JACOBS et al. (1972) at least 6% of all recognized conceptions seem to have an abnormal chromosomal constitution, but only approx. 0.5% may come to birth (Fig. 2, Table 3). BOUÉ et al. (1973) observed 921 (= 61.4%) chromosomal anomalies in 1,500 abortuses of the first trimenon. Similar percentages were obtained in a current prospective study of the Deutsche Forschungsgemeinschaft (DFG) concerned with "Pregnancy course and child development":

Up to April 1973 in a total of 13,948 pregnancies 1,341 (9.6%) spontaneous abortions were documented. Out of these, 180 spontaneous abortions could be analysed cytogenetically, i.e. 182 karyotypes resulted because of twinning in 2 cases. Karyotypes of the twin abortions were normal; for statistical reasons they were counted as two normal ones. 128 spontaneous abortions showed normal karyotypes, 52 had chromosomal aberrations (28.8%). The sample was subdivided into 70 early abortions up to the 13th week of pregnancy and 110 late abortions. The rate of chromosomal aberrations was

in early abortions	33 = 47.1%
in late abortions	19 = 17.3%.

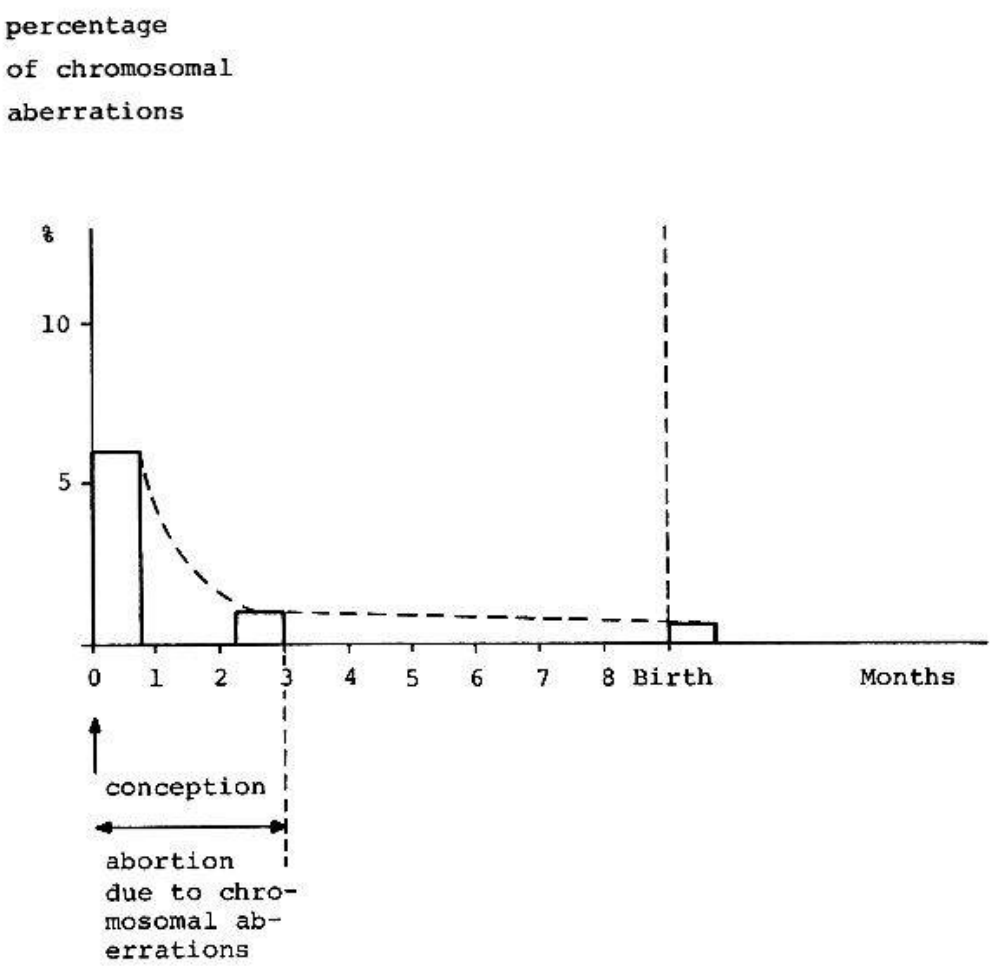

Fig. 2. The incidence of chromosomal aberrations in prenatal and postnatal life.

Table 3

Incidence of chromosomal anomalies in newborn surveys (consecutive hospital births) according to P. A. JACOBS et al. (1972)

	Numerical aberrations	Structural aberrations	Total live births
Autosomal	trisomies (21, 18, 13 and others) 0.13%	0.18% balanced translocations = 5/1 non-balanced	0.31%
Gonosomal	XO, XYY, XXY, XXX etc. 0.2%	0.008%	0.21%
Overall			0.52%

The distribution of types of chromosomal anomaly in comparison with the observations of BOUÉ et al. (1973) is as follows:

	Prospective study DFG		Boué et al.	
	n	%	n	%
Trisomies	27	51.9	495	53.7
Monosomies	11	21.2	141	15.3
Mosaics	7	13.5[1]	10	1.08
Polyploidies	5	9.6	240	26.04
Structural Aberr.	2	3.8	35	3.8
Total	52	100.0	921	100.0

[1] Incl. possible pseudo-mosaics because of growth of maternal normal cell lines.

The seeming discrepancy between the results of these series needs further clarification. In cases where the embryo was present development usually stopped around the 4th to 6th week p.conc. About 70% of those embryos which stopped developing before the 4th week p.conc. were malformed. Similar malformations are common to embryos with different karyotypes.

All autosomal and gonosomal numerical aberrations, but only 25% of structural anomalies are new mutations. From the data available so far, the rate of chromosomal aberrations due to new mutations has been calculated at 1.85×10^{-3} per gamete/generation. This may be underestimated.

Phenogenesis in specific chromosomal aberrations still remains largely obscure. Characteristic malformation syndromes can be related to specific numerical or structural anomalies, but single anatomical deviations from the normal range of variation seem to be quite non-specific. It is obvious that the normal command of the genome over embryonic development is disturbed by the lack or the addition of functionally important chromosomal material. This concerns whole chromosomes as well as parts of chromatids. Vogel (1973) pointed out the importance of bands and interbands of chromosomes as functional units of gene action. He formulated the hypothesis that "the main clinical symptoms of the syndromes caused by numerical or structural chromosome aberrations in man are not caused primarily by aberrant numbers of classic structural genes, but by disturbances in the function of DNA with control function".

1. Autosomal aberrations

According to Jacobs et al. (1972) the incidence of autosomal chromosomal anomalies is as follows:

Numerical 0.13% Structural 0.18% Total livebirth 0.31%.

Only a few types of autosomal numerical aberration may be compatible with intra-uterine development and live birth. Up to now they predominantly concern 3 trisomies, of which only one, i.e. trisomy 21, may be compatible with further development after birth. Trisomy 21, characterized by the

phenotype of Down's syndrome, is of considerable practical importance because the viability of the patients can be improved by care. This syndrome accounts for nearly one third of all severely subnormal children. The incidence in the DFG prospective study was 15:9,770 total births = 0.15%.

A cytogenetic classification of trisomy 21 can be made as follows:

- The regular trisomy 21 (3 free chromosomes 21):
  approximately 93% of all cases
- Mosaics normal cell line/trisomy 21 cell line:
  approximately 2% of all cases
- Centric fusion trisomy 21 with a D/G (predom. 14/21) or a G/G (21/22 or 21/21) translocation chromosomes:
  approximately 5% of all cases
- Partial trisomy 21:
  extremely rare

The condition of trisomy G in relation to clinical symptoms similar to the Down syndrome has recently been observed in the non-human primate, a female chimpanzee (Pan troglodytes).

Trisomy 13 (the Patau syndrome) and trisomy 18 (the Edwards syndrome) are semilethal; the aberrations are correlated with characteristic malformation syndromes.

Structural autosomal aberrations may be of clinical and social importance as they concern characteristic malformation syndromes that may be compatible with life and that are associated with mental imbecility.

Specific deletions in relation to well-defined syndromes are:

	Incidences
5p– (the "cri du chat" syndrome Lejeune)	1:50,000
4p– (the Hirschhorn-Wolf-syndrome)	1:500,000

18p– or 18q– (syndromes de Grouchy I or II) Observations in single cases.

The Philadelphia chromosome (Ph 1) correlated with acute myeloblastic leukaemia is in fact a chromosome 22 with a deletion in the distal parts of the long arms. The partial trisomies 8p or 8q, 7q, 9p, 22q– are observations in single cases. They, too, seem to be recognizable as specific malformation syndromes.

Somatic structural mutations concern chromosome or chromatid breaks and chromosome reunions, closely related to six inherited diseases: Fanconi's anaemia, Bloom's syndrome, ataxiatelangiectasia, glutathione reductase deficiency, Kostmann's agranulocytosis and pernicious anaemia. The cytogenetic data are by no means uniform; in each disease, the incidence of leukaemia is increased. According to SCHROEDER (1973) a change in the genetic material itself may create primary, yet unknown conditions for malignant growth.

2. Gonosomal aberrations

According to JACOBS et al. (1972), the incidences are as follows: numerical 0.2%, structural 0.008%, total livebirth 0.21%. Karyotypes 47,XXY and

47,XYY are predominant (approx. 1:900 of male births for each aberration), but they cannot be reliably recognized clinically before puberty. The relationship between X polysomies and specific syndromes depends mainly on the inactivity of the supernumerary X chromosomes. M. LYON's hypothesis of X inactivation in the female around the 16th day p.conc. nowadays may be understood as an incomplete inactivation of one or both X chromosomes mainly in the short arms, where the genes regulating whole-body growth are located.

The 45,X chromosomal constitution leads to the characteristic Turner's syndrome and may be recognized at birth. According to JACOBS et al. (1972) only one case in 9,456 female newborns has been found, but the incidence in spontaneous abortions is about 40 times as high.

Nine cases of triple X females in 9,456 female newborns have been observed by JACOBS et al. (1972); they are increasingly liable to psychosis in later life, otherwise they seem to be normal with their fertility intact. They may give birth to a child with the 47,XXY constitution.

In all the gonosomal numerical aberrations, mosaic mutations, with two or more cell lines either in combination with a normal cell line or with different aberrant cell lines only, could be observed. They are related to a high degree of variability in clinical manifestations. Structural gonosomal aberrations are very rare. They are only important as far as they concern the localization of specific functional gene sites; i.e. the localization of sex-determining factors on the Y chromosome.

SIEBERS et al. (1973) concluded from their comparative analysis of all cases so far observed that the genes for the initiation of testicular development are located on the proximal part of the long arm of the Y chromosome, while the genes responsible for the maturation of the testis are localized on the short arm of the Y chromosome.

3. Factors favouring the occurrence of chromosomal aberrations

Meiosis in the female already starts before birth; homologous chromosomes join in meiotic prophase and rest in dictyotene, for 2 or 3 decades, until the germ cell is stimulated to finish meiosis. During the long time of rest the pairs of chromosomes might be influenced by a variety of exogenous agents, i.e. X-irradiation, cytostatic or antimitotic chemicals and viruses. From this point of view, the increased rate of meiotic non-disjunction leading especially to trisomy 21 in the offspring of late pregnancies is readily understandable. In the male germ cells, meiosis starts at puberty and then continues. It has been shown in the male also that non-disjunction may occur in meiosis and may result in a conceptus with a regular trisomy 21.

Mitotic postconceptional non-disjunction may occur spontaneously or may be influenced by exogenous agents. This has been shown in experimental investigations with hamsters and mice (YAMAMOTO and INGALLS, 1972; ROEHRBORN and HANSMANN, 1973).

4. The value of chromosome studies

a) Possibility of an autosomal chromosomal aberration

- Differentiation of a chromosomopathy syndrome from monogenic multifactorial or exogenous causes
- Verification of trisomy 21
- The cause of multiple spontaneous abortions may be a reciprocal translocation in one of the parents
- Detection of the Ph 1 (22q–) in myeloid leukaemia
- Verification of a preleukaemic inherited disease by the detection of chromatid or chromosome breaks and rearrangements or pulverization.

b) Possibility of a gonosomal chromosomal aberration in certain endocrine disorders

- Intersexual external genitalia in the newborn, all types of intersexuality in children and adults (exclusion of adrenogenital syndrome)
- Inguinal hernia in females (exclusion of testicular feminization)
- Retarded puberty in females of small stature
- Primary amenorrhoea
- Retarded puberty in males with small testes and mental retardation
- Small testes and/or sterility
- Overgrowth and psychosyndrome

In the case of an inherited chromosomal aberration chromosome studies in members of the family may help to prevent the birth of malformed children. Empirical-risk data are available with regard to the relationship between maternal age and specific chromosomal aberrations.

Long-term administration of cytostatic drugs or the application of X-rays particularly around conception may also be an indication for chromosomal analysis. The application of modern techniques of chromosome banding is necessary for the detection of more subtle structural defects. Finally, chromosome studies can help to elucidate changes in the rate of chromosomal aberrations in special risk groups in comparison with the general population (census study).

D. Methods and results of human epidemiology

The main object of epidemiological studies is the detection of causal associations between aetiological factors and congenital malformations in human populations. These investigations are performed by two different approaches: the retrospective and the prospective inquiries.

1. *The retrospective inquiry* starts with the birth of a malformed child. The history of the mother is examined and unusual events which occurred during the pregnancy are investigated to assess their possible aetiological relation to the malformation. Such inquiries performed systematically on large samples may point to a common factor and may reveal a particular

agent to be a teratogen. In addition, experimental studies may assist in confirming its implication.

The retrospective inquiries have already yielded a number of valuable positive results. GREGG (1941) and SWAN et al. (1943) showed in this way that rubella was responsible for malformations which hitherto had been considered to be hereditary. In 1961, LENZ in Germany and MCBRIDE in Australia reported a possible connection between the use of thalidomide and the increase in certain previously rare malformations concerning chiefly the limbs in newborn babies. Animal experimentation supported this and statistical analysis performed on large samples of the population showed a clear correlation between the increase in the incidence of severe limb malformations and the use of thalidomide between 1959 and 1962.

2. *The prospective method* excludes the element of bias inherent in retrospective studies. The inquiries begin with gestation; every drug prescription and possible infections are recorded during the pregnancy, which makes the collected data more objective. But it is difficult to pursue them: enormous numbers of cases must be examined before a reasonable number of malformations for statistical treatment is encountered. For instance, in order to get information about 100 spinae bifidae, the investigation should comprise more than 100,000 pregnancies. Therefore, such prospective studies must be undertaken on a national multiregional scale in a number of countries.

For instance, a recent survey in Scotland showed that during pregnancy, over 97% of 1,369 women had taken prescribed drugs and 65% unprescribed drugs (NELSON and FORFAR, 1971). It was found that significantly more of the mothers who gave birth to children with congenital malformations had taken drugs than mothers in the control group.

A prospective epidemiological study by the French Ministry (SPIRA et al., 1973) on 20,000 women examined in the 3rd month of pregnancy and whose children had been observed at birth and one year later, yielded the following results: 9,566 women had taken various sex hormones (progesterone, progestogens, and synthetic oestrogens). They were compared with a control group of 8,387 women who had taken no drugs. The statistical analysis was made on the entire group of sex-hormone-treated women, and on individual groups who took only progesterone compounds, oestrogen compounds, or a combination of oestrogens and progestogens.

In each of these groups the percentage of congenital malformations was different from that found in women who had not taken sex hormones during their pregnancy.

DEGENHARDT and KOLLER (1973) have analysed a prospective multiregional investigation which was initiated in 1963 by the "Deutsche Forschungsgemeinschaft". Of 5,800 pregnant women, 1,098 (18.9%) did not use any drug during the first trimester of pregnancy. For evaluation, 61 subgroups were distinguished according to the drugs mostly used during the first trimester of pregnancy. Phenacetin, tranquillizers, and five single drugs have been chosen for special analysis: they are acetylsalicylic acid, ethyl-

phenylephrine, meclizine, diazepam, and a combination product containing progestogen and oestrogen.

Until now, no association has become apparent and these results are being reassessed in a larger sample of pregnant women. Such studies should lead to a better knowledge of the teratogenic danger of drugs in human populations.