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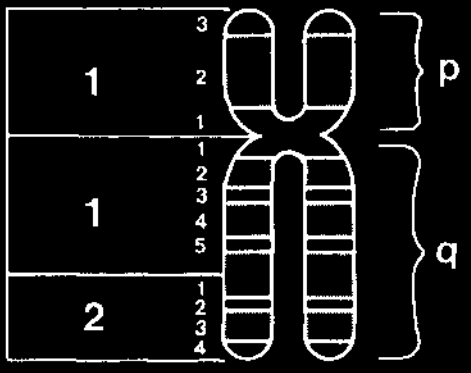
Birth Defects and Genetic Counseling



VA Monograph
October 1985

Birth Defects and Genetic Screening and Counseling

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October 1985

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PREFACE

Worldwide attention continues to be focused on the possible adverse health effects, including birth defects, which may result from human exposure to the phenoxy herbicides and dioxins. Many veterans of the Vietnam Conflict, together with their families, remain concerned that their exposure to Agent Orange has significantly increased the risk of having children with congenital abnormalities. This monograph has been prepared as a basic information resource for physicians and other health care professionals who have no special expertise regarding the etiology of birth defects. At the very least, it is anticipated this monograph will serve to assist these individuals in attaining a greater understanding of the science of genetics and the possible relationship between potentially toxic chemicals in the environment and birth defects. It is especially important that all individuals who were involved in discussing such concerns with veterans and their families be as well informed as possible in this complex and often emotionally charged area.

Recent significant research has contributed substantially to the body of knowledge describing what relationship, if any, exists between birth defects and military service in Vietnam. Two major studies, an Australian government sponsored study and a study conducted by the Centers for Disease Control, Atlanta, Georgia, completed in January 1983 and August 1984, respectively, are important milestones in the search for answers to these questions. Executive summaries of both of these research efforts are included in the appendix of this monograph.

It is readily understood that no single publication such as this monograph, nor any single research effort can stand alone or provide final answers to the complex health issues related to the etiology of birth defects. Nevertheless, it is hoped that the cumulative weight of this and other publications and the results of verifiable and credible research will assist health care professionals in serving the needs of individuals who are concerned about the likelihood of having children with birth defects and the impact of this on their personal lives. It is the goal of this monograph to help health care professionals to deal more effectively with this difficult issue.

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The Veterans Administration thanks the many individuals who were involved in the conceptualization and preparation of this monograph.

Appreciation is particularly extended to the monograph's author, Annemarie Sommer, M.D., Associate Professor of Pediatrics, Director of Genetics Section, Children's Hospital, Columbus, Ohio, who is to be congratulated for the quality and scope of the final product and for her close support to the staff of the VA Agent Orange Projects Office, Department of Medicine and Surgery, in the development and successful completion of this project.

Mention must be made of Thaddeus E. Kelly, M.D., Ph.D., Professor of Pediatrics, University of Virginia Medical Center, Genetics Section, Charlottesville, Virginia, who served as the primary reviewer of the monograph and whose assistance, in this regard, was of invaluable support in the refinement of this publication.

Recognition is extended further to Dr. Barclay M. Shepard, Director, Agent Orange Projects Office (AOPO) and Dr. Lawrence B. Hobson, Deputy Director, for their guidance of this effort and to the following present and former members of their staff who were intimately involved in coordinating or assisting in the preparation of this publication: Lt. Col. Alvin L. Young, (USAF), Specialist in Environmental Sciences, Office of Director; Mr. Layne A. Drash, Chief, Administrative Section; Mrs. Elaine M. Morrow, Budget Analyst; and to the following clerical support staff in the Administrative and Research Sections, AOPO: Mrs. Paula Piersall, Mrs. Sharon E. Kurtz, Mrs. Willie Toye, Ms. Janice Martin, and Mrs. Barbara Brandau.

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Chapter 1

Overview

Magnitude of Genetic Problems

As health care has improved certain aspects of medicine have become more important. The advent of antibiotics, for example, made it possible to prevent, treat, and cure many illnesses that had earlier caused significant morbidity and mortality. Because of such medical advances, disorders due to birth defects and genetic disease have assumed greater prominence within the spectrum of today's health problems.

Handicapping conditions, many of which are due to genetic defects, have captured significant public interest. Because of the magnitude of the problem, Public Law 94-142 was enacted in 1975 mandating education for all handicapped persons.

In most cases, conditions causing malformations first become apparent in infancy or childhood. It is estimated that approximately 5% of all newborns have birth defects, 3% of which are major malformations. Because of this, up to one-third of all admissions to pediatric institutions are for birth defects, congenital malformations, or other conditions having a genetic component.

Genetic disease involves all racial and ethnic groups throughout the world. McKusick's Catalog of 1983 cites 3,368 known inherited conditions, which 1,827 are autosomal dominant traits, 1,298 are autosomal recessive disorders, and 243 are X-linked conditions. It is estimated that approximately 7.5% of all congenital malformations stem from monogenic disorders.

Although specific genetic diseases may be rare, as a group they account for a significant number of handicapping conditions. The better known genetic disorders are, of course, commoner ones. Examples are: Sickle cell disease, 1 in 625 blacks; polydactyly, 1 in 1,000 whites and 1 in 100 blacks; cystic fibrosis, 1 in 2,500 whites; hemophilia, 1 in 2,500 males; neurofibromatosis, 1 in 3,000; phenylketonuria, 1 in 15,000; Marfan syndrome, 1 in 66,000; and Duchenne muscular dystrophy, 1 in 100,000 males.

Another category of birth defects leading to congenital malformations are the chromosomal disorders, which occur in approximately 1 in 150 or 0.6% of all liveborn children. They are present, however, in approximately 6% of all children born with serious malformations.

The magnitude of the problem can also be measured by the incidence of mental retardation. It has been determined that approximately 70% of all mentally retarded people have problems due to genetic causes.

Causes of congenital malformations include a variety of maternal diseases. Infectious diseases in the mother in the first trimester such as rubella, toxoplasmosis and

cytomegalovirus, may account for 2% of congenital malformations in the offspring. The proportion of malformed children born to mothers who have diabetes mellitus is 1.4% . Another 1.2% of children born to epileptic mothers may have birth defects, and less than 0.5% of malformations may be related to other maternal illnesses.

It has been recognized that with today's improved health care, many infants and children who were formerly considered to have a lethal condition can now be saved. The impact of birth defects and genetic disorders is still significant, however. Approximately 21% of infant mortality is due to congenital malformations. Although the specialty of medical genetics is relatively young, great progress has been made. Through early recognition and treatment of genetic diseases, together with the growing practice of genetic counseling, it is hoped that the resultant human suffering will in time be greatly diminished.

History of Medical Genetics

It is generally accepted that modern genetics started with the work of the Austrian monk Gregor Mendel (1822-84), who published his findings on plant genetics in 1865. Although other work followed, it was not until Archibald Garrod (1858-1936) coined the term "inborn errors of metabolism" around the turn of this century that a significant further step in the understanding of human genetics was taken. He studied alkaptonuria and through the study of family pedigrees is credited with describing this disease as an autosomal recessive condition.

Immunogenetics, which includes the study of blood groups, also began around the turn of the century. In 1909, Landsteiner demonstrated the ABO blood groups, but it was not until 1941 that the Rh blood types were discovered. In 1943, a study by Avery, McLeod, and McCarthy showed that the chemical makeup of genetic material is deoxyribonucleic acid (DNA). In 1962, Watson and Crick received a Nobel Prize for demonstrating DNA's structure. The genetic code embedded in this structure was deciphered by Nirenberg, Ochoa, Khorana, and others for which they received a Nobel Prize in 1968. About the same time, immunogenetics advanced further with the discovery of HLA, a major histocompatibility complex in humans. The first serologic methods to detect HLA were developed by Dausset and the specific gene loci for the HLA complex were assigned to the short arm of chromosome number 6 in 1977 by Francke.

Chromosomes were first identified by Walter Flemming in 1877. Further work by Hamerton and Ford in 1956 resulted in the discovery that the correct diploid number of chromosomes in human cells is 46.

The first documented chromosome abnormality was trisomy 21, the abnormality found in Down syndrome, described in 1959 by Lejeune. Since then many other chromosomal disorders have been discovered and described.

In 1968, Casperson et al., described quinacrin fluorescent staining. This, as well as other methods of banding chromosomes, resulted in improved delineation of chromosome errors and clinical phenotypes since banding allows for identification of individual chromosomes and parts of chromosomes.

With the discovery and perfection of banding techniques, chromosome mapping had its beginning. In 1968 the first specific gene was assigned to an autosome by Donahue, who was able to document that the Duffy blood group is located on chromosome #1. At present approximately 450 gene loci have been mapped on specific chromosomes, and because of intense research in this area the number is constantly expanding.

Another development in genetics occurred in the late 1950s with the development of human fibroblast cell cultures from skin biopsies. Documentation of the ability of human fibroblasts to reflect genetic conditions has led to the use of fibroblast cultures for the study of many diseases. The establishment of the mutant cell bank as a resource of cultures for cytogenetic and biochemical studies has aided further research. Procedures that have been accomplished through fibroblast cultures include cloning and hybridizations, as well as the exploration of cytogenetic errors and enzyme defects. No doubt, the development of new techniques for gene localization by means of the specific enzymatic digestion of DNA and the isolation of specific DNA segments will ultimately lead to a fuller understanding of human genetic disease and will assist in the treatment of many disorders.

Chapter 2

Mendelian Genetics

Mendelian disease comprises all single gene disorders. Mendelian genetics was first delineated by the Austrian monk Gregor Mendel, who presented some of the results of his experiments with peas in 1866. He found that certain characteristics were transmitted from one generation to the next unchanged, while other characteristics became latent. Those "characters," as Mendel named them, were later called "dominant and recessive traits," the unchanged characters being dominant and those that became latent, recessive. Traits are those characters observed by Mendel as perceivable features in the organism.

The Pedigree

One part of a genetic evaluation is the construction of a pedigree. Here a family history is depicted in graphic form. A pedigree starts with conventional symbols used to designate the sex of an individual, mating, twinning, abortions, and other situations. The patient or family seeking genetic counseling and analysis is usually designated on the pedigree as the index case and the pedigree is constructed from there (Figure 1).

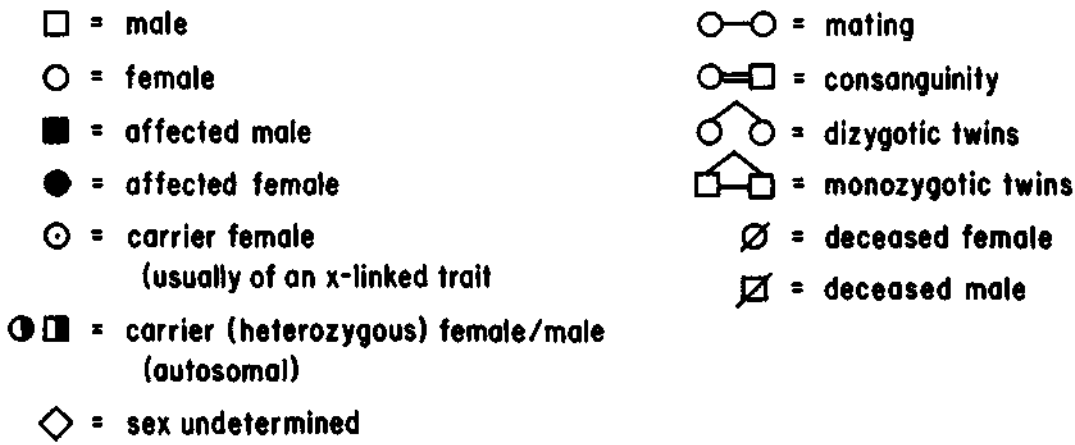

Figure 1. Pedigree symbols

Eliciting the family history and constructing the pedigree is important in order to obtain complete information, which must include details, not only about brothers and sisters, parents and grandparents, but also about neonatal deaths, deaths during childhood, miscarriages, and stillbirths. In addition, the pedigree must contain data about such occurrences as birth defects, mental retardation, deformities, and unusual stature as well as other specific abnormalities that may be present in the family. It is from the careful analysis of a family history that a physician may be able to provide genetic counseling. But even if a pedigree does not reveal other affected persons, a genetic disorder cannot be ruled out and the specific diagnosis of the index case only is the determining factor.

Autosomal Dominant Inheritance

A trait that occurs through several generations in a family may be due to an autosomal dominant gene. This trait stems from a single mutant gene located on an autosome. Approximately 1,500 autosomal dominant traits are listed in McKusick's *Mendelian Inheritance in Man.* The phenotypical expression of these traits may vary in their clinical minifestations and may, therefore, be termed variable expressivity. Autosomally transmitted traits may also lack penetrance, which implies the absence of any clinical expression at all. This is probably a rare occurrence in human dominant conditions but may at times explain the "skipping" of an individual in a pedigree that otherwise clearly documents dominant inheritance. Individuals who appear not to manifest a given trait must be examined very carefully since often some expression of the trait has usually been missed. Autosomal dominant conditions that are characterized by their occurrence in several generations are relatively common (Figure 2).

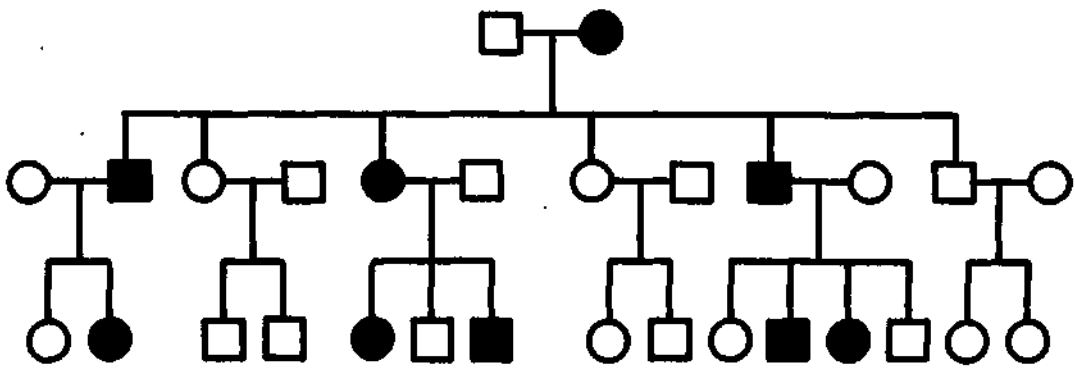

Figure 2. Autosomal dominant pedigree

One example is the *Waardenburg syndrome* (Figure 3 a, b, p. 29) an autosomal dominant syndrome characterized by pigmentary changes such as heterochromia of the iris, white patches of hair or a forelock, and depigmented patches of skin. Other signs include lateral displacement of the medial canthi and sensorineural hearing loss. In some individuals the only expression of the Waardenburg trait is a white forelock that may be overlooked by examiners.

Another autosomal dominant disorder is *Marfan syndrome,* a connective tissue disorder. Individuals with Marfan syndrome (Figure 4 a, b, p. 30) usually have a slender build with long extremities and unusual body proportions. The armspan exceeds the total height. Affected individuals have arachnodactyly (spider fingers) and hyperextensibility of joints. Other manifestations include dislocation of the lenses and other eye abnormalities, as well as cardiovascular problems such as mitral valve prolapse and aortic aneurysm. The latter frequently leads to premature death.

Neurofibromatosis is a relatively common autosomal dominant disorder occurring with a frequency of 1 in 3,000 individuals (Figure 5, p. 31). The main manifestations include multiple neurofibromata, cafe-au-lait spots, and bone lesions. Frequently, the diagnosis can be confirmed in a child by the presence of six or more cafe-au-lait spots 1.5 cm or more in size. Axillary freckling may also occur. Another presentation is the occurrence of a congenital pseudarthrosis of an extremity. Neurofibromata can be observed as subcutaneous masses along peripheral nerves, but may occur in the central nervous system as well. Neurologic manifestations appear as brain tumors, tumors involving the optic and acoustic nerves, and seizures.

The family pedigree of a patient with neurofibromatosis may document the occurrence of this dominant trait in several other family members, but a negative family history should not dissuade the clinician from making the diagnosis since the mutation rate in neurofibromatosis is high.

The most significant characteristics of autosomal dominant inheritance are:

1. The trait occurs in successive generations.

2. The abnormal trait is expressed as an abnormality that may be observed in the affected individual.

3. An affected individual will transmit this trait to 50% of his offspring.

4. Autosomal dominant conditions occur with equal frequency in males and females.

5. An unaffected individual does not transmit the trait to his offspring.

Autosomal Recessive Inheritance

There are approximately 1,100 known autosomal recessive disorders. Most commonly, they are metabolic disorders with very few, if any, dysmorphic features. Examples are specific

disorders with a higher frequency in certain ethnic groups such as β-thalassemia in Mediterranean people, hemoglobin S-thalassemia in Africans, and Tay-Sachs disease and familial dysautonomia in the Ashkenazi Jewish population.

Since each autosomal gene in the human occurs doubly, the effects of a single abnormal or mutant gene may not be evident when its paired gene is normal. Such a mutant gene is therefore considered recessive because its partner or allele on the other chromosome of the given pair performs the required normal function adequately. If both genes at the same locus on a pair of homologous chromosomes determine the same abnormal characteristic, however, an abnormal state results.

For example, in a disorder due to an enzyme deficiency, the heterozygous carrier of the trait will have 50% enzyme activity, which is adequate to meet metabolic needs, but the affected homozygous individual will be totally deficient in enzyme function. It is a double dose of the same abnormal gene, one of which is derived from each parent, that accounts for the disorders of an autosomal recessive nature. There are, however, some autosomal recessively inherited syndromes characterized by malformations.

A syndrome of congenital anomalies is the *Thrombocytopenia-absent-radius syndrome* (TAR) (Figure 6 a, b, p. 31), which in the newborn may be easily recognized by upper extremity malformations. Most commonly the infant will have forearm malformations secondary to an absent radius with the presence of a full five-digit hand. In addition, multiple petechiae and bruises may be observed because of a greatly decreased platelet count, often below 10,000. Infants are at great risk of bleeding episodes such as gastrointestinal, CNS, and pulmonary hemorrhages. As a rule, the platelet count stabilizes and bleeding declines with increasing age. The absent radius may be the only telltale sign of this autosomal recessive disorder.

Hurler syndrome (mucopolysaccharidosis IH or MPS IH) (Figure 7 a, b, p. 32) is another example of a recessive disease. The basic defect is a deficiency of the enzyme ∂-L-iduronidase which is responsible for the abnormal storage of material in lysosomes that leads to progressive deterioration. Hurler syndrome does not become clinically evident until the end of the first year of life. Then macrocephaly, growth deceleration, corneal infiltration, and hepatosplenomegaly become evident. There is associated progressive neurologic deterioration, and death occurs by 10 years of age.

Tay-Sachs disease is a neurodegenerative disorder most common among Ashkenazi Jews. The disease is the result of hexosaminidase, a deficiency that leads to storage of a ganglioside in brain cells. Clinical signs and symptoms appear around four to six months of age and include deceleration of development, hypotonia, opisthotonus, seizures, and hyperacusis. A cherry red spot in the macula may be observed and is a vital diagnostic clue. Death occurs at three to five years.

Characteristics of autosomal recessive inheritance (Figure 8) are:

1. The disorder occurs in sibships only and is not seen in successive generations.

2. Parents who are carriers of the same abnormal genes have a 25% chance with each pregnancy of having an affected child.

3. The disorder occurs with equal frequency in males and females.

4. The effect of consanguinity is to increase the risk of an autosomal recessive disorder.

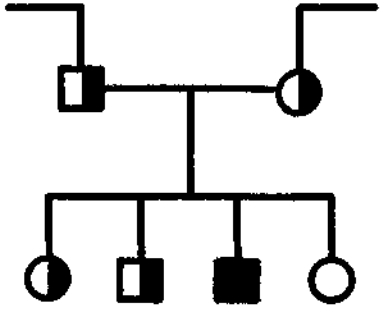

Figure 8. Autosomal recessive pedigree

X-linked Inheritance

X-linked inheritance refers to genes located on the X chromosome. Over 100 genes are known to be present on the X chromosome.

Mutant or abnormal genes on an X chromosome in a single dose may be expressed as a significant abnormality in males only. Since males have just one X chromosome, the abnormal gene may be expressed because there are no comparable genes on the Y chromosome.

The disorders occurring in males only are called X-linked recessive disease. Male offspring are severely affected, but the carrier mother may be detected only by special laboratory tests if at all. The father does not carry the trait.

Some of the more common X-linked recessive disorders are hemophilia, Duchenne muscular dystrophy, X-linked hydrocephalus, and the Lesch-Nyhan syndrome.

Another example of an X-linked recessive disorder is *Menkes syndrome* (Figure 9 a, b, p. 33). This abnormality of copper absorption results in very low copper levels, with severe clinical consequences. Its boy victims have light-colored, fragile hair which reveals monilethrix microscopically and provides the diagnostic clue. There is progressive neurologic

degeneration, with death in early childhood. Angiography shows multiple areas of vascular tortuosity also due to the severe copper deficiency.

The features of X-linked recessive inheritance (Figure 10) are:

1. Severe disease occurs in males only.

2. The trait is transmitted through carrier females.

3. There is no male-to-male transmission.

4. Carrier mothers face a 50% chance that each of her sons will be affected. Although all daughters will be clinically normal, 50% will be carriers.

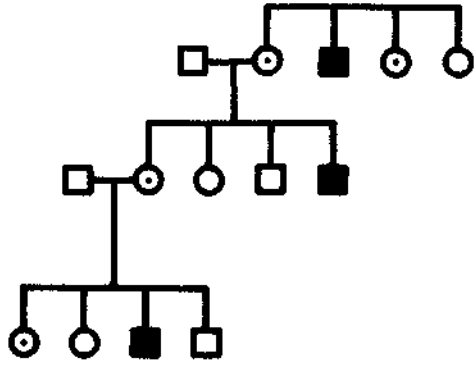

Figure 10. X-linked recessive pedigree

Only a few conditions are thought to be X-linked dominant. These rare disorders are for the most part lethal in the male fetus, and only females are carriers. Examples of this form of inheritance are the Oro-Facial-Digital syndrome Type 1, Goltz syndrome (focal dermal hypoplasia), and Incontinentia Pigmenti.

An abnormal dominant gene located on an X chromosome will result in the following:

1. A mother carrying the X-linked dominant gene will transmit it to half of her female offspring, who will also be affected.

2. Fifty percent of all male offspring of an affected mother will be affected. They will be spontaneously aborted because of fetal death or if born alive, will be severely affected. Females are less affected.

3. Half of the daughters and half of the sons of a mother carrying an X-linked dominant gene will be normal, and since they do not carry the abnormal gene they will not transmit it to later generations.

Chapter 3

Multifactorial Causation

The terms "multifactorial" and "polygenic inheritance" are frequently used interchangeably, but multifactorial causation is probably more appropriate. Polygenic inheritance implies that only multiple genes with small additive effects determine the presence of a trait, while multifactorial causation refers to more than one factor being responsible for the development of a physiologic trait or clinical disorder. Multifactorial causation explains not only some disorders which have a tendency to run in families, but also normal human variation.

Examples of continuous normal human variations are stature, blood pressure, and number of ridges in a fingerprint. They are best represented by a normal (Gaussian) distribution curve, which is the result of a number of factors, some acting in one direction, some in the other, the total effect being additive. Both groups of genes as well as environmental influences are therefore determinants in multifactorial causation and the final effect is the sum total of the individual constituents.

Most common single birth defects are best explained on the basis of multifactorial causation, as evidenced by an increased incidence in relatives. The specific clinical picture represents the cumulative effect of many genes with small positive or negative influences. The exact number of contributing genes is not known but it is not a matter of simple addition and subtraction; there is also a threshold phenomenon. The net effect of the adverse genes will not be obvious unless it exceeds a critical threshold value beyond which the severity will be directly proportional to the number and degree of influences of the detrimental genes.

The threshold phenomenon for multifactorial causation is that level of combined genetic and environmental influences at or beyond which the influence becomes obvious. This may be explained by an analogy in which the genetic factors contributed by each parent are represented by glasses partially filled with water, with the water level below the threshold.

As the water from both parents is poured into the glass of the offspring, the water level may reach the threshold. If environmental factors, represented by a rock are added to the glass, the threshold is exceeded, the water spills over, and the clinical trait becomes obvious in the child (Figure 11).

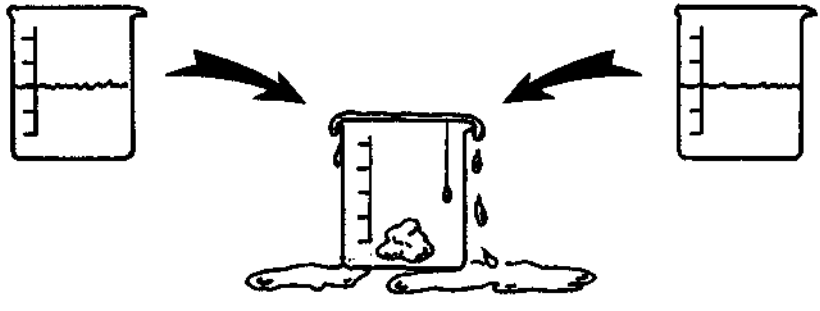

Figure 11. Multifactorial threshold phenomenon

Another factor considered in multifactorial inheritance is the number of genes shared by relatives. It stands to reason that the more genes are shared, the more likely it is that a given trait will recur. This is characteristically seen in multifactorial inheritance, where the highest risks exist for close relatives and where the risks decline rapidly the more distant the relationship between individuals.

The most important factors in the evaluation of birth defects, therefore, are a good family history and physical examination. These will distinguish between other forms of inheritance, other syndromes, and those birth defects due to multifactorial causes. Some examples of multifactorial defects are:

1. Isolated cleft palate: Incidence, about 1 in 1,000. More frequent in females than males. Not to be confused with cleft lip/cleft palate complex.

2. Cleft lip/cleft palate: Incidence, 1 in 1,000. Multifactorial. One of the most frequent situations for which genetic counseling is sought.

3. Neural tube defects: Incidence in United States, about 1 in 1,000. Includes anencephaly, encephaloceles, myelomeningoceles.

4. Hydrocephalus: Incidence, 1 in 1,000.

5. Congenital heart disease: Incidence, 6 to 8 in 1,000.

6. Clubfoot: Incidence, 1 in 1,500. More frequent in males than females.

7. Congenital hip dysplasia (including dislocation): Incidence, 1 in 1,000. More frequent in females.

8. Congenital scoliosis: More frequent in females. Often not apparent until some years after birth. Continuous examinations necessary.

9. Pyloric stenosis: Incidence, about 1 in 500 with high incidence in males.

10. Hirschsprung disease: Congenital aganglionic megacolon.

11. Mental retardation of moderate severity (IQ of 70).

12. Urinary tract malformations: Very common. Often not detected. When a urinary tract anomaly is found in an individual, other current and future family members are sufficiently at risk to necessitate obtaining a careful family history and probably a screening intravenous pyelogram.

Multifactorial causation is likely if the condition is relatively common. Families have an increased risk compared to the general population for recurrence of the disorder among first-, second-, and third-degree relatives of the affected person.

Multifactorial causation is operative for most common single congenital malformations, while the occurrence of two or more birth defects—even if alone they may be multifactorial—suggests another etiology.

The baseline risk for first-degree relatives of the affected proband is 2% to 5%, and about half that for second-degree relatives. After two affected offspring the risk increases two- to three-fold to as much as 10% to 15% and increases further with each additional affected offspring. Recurrence risks are higher for first-degree relatives and decreases significantly the more distant the degree of relationship to the index case.

Chapter 4

Chromosomes

Chromosomes are the structures in the cell nucleus which contain genes. They are only visible during cell division. In chromosome disorders, instead of a single gene, a whole group of genes produces an effect. This results in an altered gene dosage instead of an altered gene product and produces a different clinical picture. There are 22 homologous pairs, which are designated autosomes. One pair, the sex chromosomes, are designated XX in the female and XY in the male.

Chromosome analysis can be performed only on dividing cells such as lymphocytes, bone marrow cells, and fibroblasts. By international convention the individually numbered autosomes are arranged in order of decreasing size and called a chromosome karyotype.

When a chromosome analysis is reported, internationally accepted designations are used. First the modal number of chromosomes is indicated (46 for a normal human). This is followed by the sex chromosome constitution (XX or XY), and finally abnormalities are described. A (+) symbol indicates additional chromosomes or parts thereof and a (−) indicates deleted chromosomes.

A normal male karyotype is therefore 46,XY and a normal female 46,XX, and a trisomy of chromosome 21 in a male is written 47,XY,+21.

With special staining techniques, chromosomes reveal individual specific banding patterns that probably reflect differences in the DNA sequence on each chromosome. The first banding technique was the quinacrine mustard method, which revealed fluorescent banding of chromosomes. Shortly thereafter, the Giemsa-trypsin technique was introduced (Figure 12a, b, p. 34). Other techniques available today are C-banding, which stains constitutive heterochromatin found around the centromere, and R-banding which is the reverse of the Giemsa-trypsin banding.

Chromosomes are also designated by their structural configuration. The most common designations relate to centromere location and to the long and short arms of the chromosome. The short arm is designated "p" and the long arm, "q." Chromosomes with the centromere at or near the middle are designated metacentrics. If the centromere is located near the end the chromosome it is called acrocentric.

When banding techniques are applied to chromosomes, the visible bands are then numbered proceeding distally from the centromere (Figure 13). An average high resolution banding technique today reveals approximately 320 bands, but in specific situations and using separate preparations up to 10,000 bands may be identified. It is through banding that individual chromosomes can be identified more accurately and translocations be more clearly delineated.

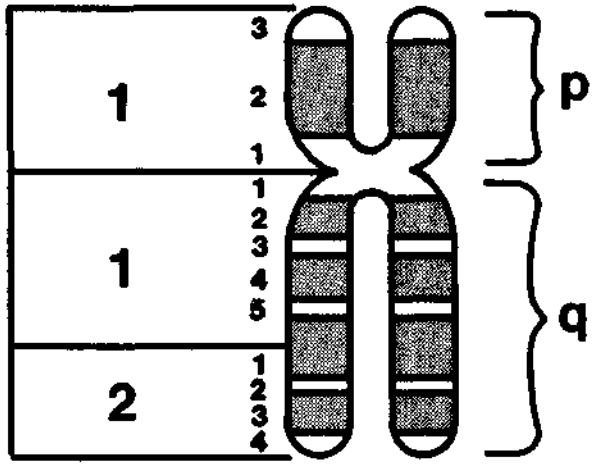

Figure 13. Single chromosome with structural designations

Cytological laboratories also use Barr body staining as a diagnostic tool. A Barr body count is usually done from a buccal smear. In the female, staining cells with an interphase nucleus reveals a small dark body near the periphery of the nucleus. This Barr body can be seen in 10% to 30% of all somatic cells from a normal woman. It represents a highly contracted X chromosome, since in each cell only one X chromosome remains genetically active while the other is inactivated and forms the Barr body.

A Barr body count may be useful in conditions with abnormal numbers of X chromosomes. The number of Barr bodies seen in any cell will always be one less than the number of X chromosomes present. For example, males and females with pure Turner syndrome have less than the number of X chromosomes normally present. For example, normal males and females with 45, X Turner syndrome have few or no Barr bodies. A male with Klinefelter syndrome may have one Barr body, and, in the triple X syndrome, two Barr bodies may be seen.

Chromosomal aberrations consist mostly of changes in chromosome number and chromosome structure. The most common numerical changes are trisomies. Except for Turner syndrome, which is a monosomy of the X chromosome, other monosomies are not thought to be viable.

Structural abnormalities usually result from chromosomal breaks. Often these breaks are followed by abnormal union of the broken ends, but if a piece breaks off from a distal part of a chromosome and does not contain a centromere, the fragment may be lost in subsequent cell

divisions. This will lead to a chromosomal deletion and an abnormal phenotype.

A chromosomal translocation is the result of at least two breaks and the subsequent union of at least two different chromosomes. Reciprocal exchange of pieces between nonhomologous chromosomes as a result of breakage usually results in a balanced translocation carrier and rarely results in a phenotypic abnormality. Unbalanced translocations may occur in an offspring of a balanced translocation carrier and produce significant phenotypic abnormalities.

Another structural alteration is the "fragile site" on an X chromosome, which may be demonstrated with special tissue culture technique. The fragile X chromosome site is an inherited trait. In patients with this trait, a site in the distal part of the long arm of the X chromosome is especially fragile and this may be expressed as an abnormal state in affected males, the most common expression being mental retardation.

Limitations of Chromosome Analysis, and When to Order Them

It is not unusual to hear people say that they want to "have their genes tested." It is one of the most common misconceptions that chromosome analysis will provide the answers to all hereditary problems. It does not. Single gene disorders cannot be diagnosed through routine cytogenetic analysis. Chromosome analysis is rarely useful in relatives unless an index patient with a chromosome aberration has been identified in the family. Nor can chromosome analysis be recommended as a screening procedure for whole populations since the incidence of unknown balanced translocation carrier status is extremely low and this would be the only indication for such a survey. Chromosome analysis should be performed, however, for specific indications. Some of them include: (1) a clinically recognizable syndrome such as an autosomal trisomy, e.g., Down syndrome, trisomy 18, or trisomy 13; (2) a clinical phenotype suggesting a sex chromosome disorder such as Turner or Klinefelter syndrome; (3) multiple system malformations, including mental retardation; (4) the occurrence of multiple miscarriages or a history of malformed infants in the immediate family; and (5) a preadolescent female with short stature.

Indications for *prenatal* cytogenetic studies of cultured fetal fibroblasts or amniocytes obtained by amniocentesis include: (1) a pregnancy in a woman who is a known translocation carrier or whose mate has been identified as a translocation carrier; (2) a pregnancy in a woman over 35 years of age, or since the incidence of a chromosomal abnormality in the offspring increases with maternal age (most of the affected children have trisomy 21); and (3) a pregnancy in a woman who has had a previous child with a chromosome abnormality.

Improved techniques and further high resolution methods may increase the indications for chromosome analysis. At present, chromosomal analysis gives answers in only a limited number of cases.

Chromosomal Disorders

Although significant numbers of chromosomal abnormalities have been identified and an infinite variety of syndromes may occur as the result of deletions and duplications, only a few have resulted in specific, recognizable clinical syndromes. Some of them are relatively rare and only a few of the better known chromosomal syndromes will be described here.

Down syndrome. In any race, Down syndrome occurs more frequently in mothers over 35 years of age. Because fewer American women over 35 years have children, however, the incidence in the United States is now approximately 1 in 1,000. Throughout Central and South America the frequency of advanced maternal age persists and the frequency of Down syndrome approaches 1 in 500.

The clinical features of Down syndrome are easily recognizable in the neonatal period. The most common physical abnormalities are absent Moro's reflex, generalized hypotonia, hyperextensibility and hyperflexibility of joints, brachycephaly, upward slanting palpebral fissures, a broad and flat nasal bridge, a flat facial profile, rather small ears, a high arched palate, and loose skin around the posterior aspect of neck. As the infant grows it develops other features that are fairly easily recognized such as relatively short limbs, decreased growth velocity, broad and short hands (particularly short fingers), small teeth and mental retardation. Although infants with Down syndrome have near normal growth parameters at birth, it usually becomes evident by the age of six months to two years that growth is slowing. Thus the average adult male height will not be more than 135 to 170 cm and the average female will be no taller than 127 to 158 cm. Infants with Down syndrome will have developmental delay and patients will fall into the range of trainable mental retardation (Figure 14, p. 35).

In addition to the physical stigmata, associated anomalies may be present. Thirty-five percent to 60% of all individuals with Down syndrome have congenital heart disease, most commonly ventricular septal defect, atrioventricular canal, atrial septal defect, patent ductus arteriosus, and tetralogy of Fallot.

Approximately 18% of all infants with Down syndrome also suffer from some form of intestinal malformation, usually duodenal atresia and stenosis, Hirschsprung disease, and annular pancreas. An increased association of Down syndrome and adolescent hypothyroidism, hyperthyroidism, and goiter also occurs. Individuals with Down syndrome also have an increased incidence of leukemia, which appears to be 10 to 20 times more common than in the general population. With increasing age, Down syndrome patients may have brain changes commonly associated with those found in Alzheimer disease. The overall life expectancy in Down syndrome is decreased and survival beyond the age of 60 years is unusual. The highest mortality occurs during the first year of life, and overall life expectancy still average's only 16.2 years. This limited life expectancy is primarily the result of congenital heart disease.

Approximately 95.5% of all children with Down syndrome have trisomy 21 (Figure 15, p. 36). The remaining 4.5% of cases are due to translocations and mosaicism. Trisomy 21 is due to an accidental nondysjunction occurring most commonly during meiosis I.

The incidence of trisomy 21 increases with advancing maternal age, especially after the age of 35. Recently developed cytogenetic techniques with banded chromosomes show that approximately 30% of all cases of Down syndrome may be due to a supernumerary number 21 chromosome of paternal origin. Trisomy 21 carries a recurrence risk of not more than 1% to 2%.

A small number of cases of Down syndrome are due to translocations. The most common one results from the translocation of a number 21 chromosome onto a number 14 chromosome. Other translocations occur between the number 21 and numbers 13, 15, 21, and 22 chromosomes. If one of the parents is found to be a balanced translocation carrier, a significant risk of having a child with Down syndrome exists. The recurrence risk will depend on the type of carrier state and whether the mother or the father is the carrier. As with all cytogenetic disorders, Down syndrome can be diagnosed prenatally by amniocentesis. The procedure should be advised in any cases of previous Down syndrome, due to translocations, or when the mother is 35 years of age or older.

Trisomy 18. Trisomy 18 was first documented as a chromosomal abnormality by Edwards in 1960. It occurs with a frequency of 1 in 4,000 live births, and the ratio of females to males is approximately 3 to 1 (Figure 16, p. 36).

Trisomy 18 is the second most common autosomal trisomy, and the physical findings at birth are significant enough to allow for early diagnosis. Some prenatal clues may include maternal polyhydramnios, reports of decreased fetal activity, and, frequently, postmaturity. Infants are usually small for gestational age. Common physical findings are generalized hypertonia, a prominent occiput, abnormally rotated and simply formed ears, small pinched facies with small palpebral fissures, a narrow palate, and micrognathia. The sternum is short and the nipples are widely spaced. A small pelvis with limited hip abduction and hypoplastic labia majora may be seen. Flexion deformities of the fingers and overlapping of the second digit over the third and the fifth over the fourth, as well as prominent heels and short dorsiflexed big toes are common (Figure 17, p. 37).

Multiple associated anomalies have been described. Among them are notable failure to thrive and mental retardation, congenital heart disease (usually ventricular septal defect, atrial septal defect, and patent ductus arteriosus), a single umbilical artery, and renal malformations such as horseshoe kidneys. There is an increased incidence of eventration of the diaphragm, inguinal and umbilical hernias, pyloric stenosis, Meckel's diverticulum and malrotation of the intestine. Infants with trisomy 18 also have an increased incidence of central nervous system malformations.

Trisomy 18 is usually lethal, half of the infants survive only two months, and only about 10% survive one year. The average survival time is three to four months. Because of the severe

developmental and mental retardation, as well as failure to thrive, even infants surviving beyond one year have a decreased quality of life. None has ever been reported to walk or talk. Trisomy 18 also occurs with slightly increased frequency with advanced maternal age. The recurrence risk is low and not more than 1% or 2%. Prenatal diagnosis can be established by amniocentesis between the 14th and 16th week of gestation.

Trisomy 13. Patau, in 1960, first documented the supernumerary chromosome in the D group, now known to be a number 13 (Figure 18, p. 38). Trisomy 13 occurs with a frequency of approximately 1 in 5,000 live births. The syndrome occurs with equal frequency in males and females and is associated with normal gestational age.

Multiple anomalies should make this syndrome recognizable at birth. The syndrome's most significant hallmarks are craniofacial malformations such as holoprosencephaly, microcephaly, a flat nasal bridge associated with a cleft lip, and cleft palate. In addition to the craniofacial abnormality, these infants may have postaxial polydactyly, congenital heart disease (most commonly septal defects), cryptorchidism in males, and hyperconvex nails. Multiple internal anomalies occur such as central nervous system malformations suggesting midline cleavage defects, renal malformations such as polycystic kidneys, duplications, and hydronephrosis, and malrotations (Figure 19 a, b, p. 38).

Trisomy 13 is a lethal genetic syndrome with a mean life expectancy of approximately 130 days, but 45% of all infants die in the first month of life and 70% are dead by three months. Survival beyond one year, though known, results in severely defective patients with very severe mental retardation. Almost all cases of Trisomy 13 are due to a pure trisomy. A small percentage of cases are due to translocations, or mosaicism. It is imperative to document the genotype of the affected individual and, in cases of translocation, to study the family. Trisomy 13 is another cytogenic abnormality that can be diagnosed prenatally through amniocentesis and fetal amniocyte culturing.

The 5p- or cri du chat syndrome. An example of a partial monosomy is the cri du chat syndrome. The "5p monosomy," "5p syndrome," and cri du chat syndrome are synonymous for a condition first delineated by Lejeune in 1963. It is a relatively rare chromosomal deletion syndrome with an incidence of approximately 1 in 50,000 live births (Figure 20, p. 39).

The name of the syndrome, cri du chat, was derived from the unmistakable cry which its victims have as newborns, resembling a kitten's mewing. This cry is due to an unusual laryngeal configuration and disappears within about a year. Other manifestations in the newborn include microcephaly, hypertelorism with a prominent forehead and downward slanting palpebral fissures. Features which should lead to a diagnosis at a later age are those described, severe mental retardation, and generally small stature. Associated malformations that may be found in children with cri du chat syndrome occur in the cardiac, renal, gastrointestinal, and central nervous systems, but none of them is consistent. Adults with the cri du chat syndrome can be recognized by microcephaly and a rather narrow face.

Chromosomal documentation is imperative. Deletion of all or most of the short arm of chromosome number 5 confirms the diagnosis. Most cases occur sporadically and carry no

significant recurrence risk, but a small percentage may be due to a chromosomal rearrangement in one of the parents. Studies of the parents are therefore indicated. Prenatal diagnosis of cri du chat syndrome is possible by amniocentesis.

The 4p trisomy. Partial trisomy for an autosome can be illustrated by partial trisomy for the short arm of chromosome 4.

Although 4p trisomy cases have been reported for several years, they were first summarized and described as a clinical syndrome by Rethore et al. in 1974. Most 4p trisomy cases result from parental rearrangement, but a few *de novo* cases have also been observed.

Most of the children are the result of normal gestation but very soon show severe postnatal growth and mental retardation. Physical findings include microcephaly, hypertelorism and other ocular anomalies, a prominent glabella and supraorbital ridges, and a flat nasal bridge with a bulbous nasal tip. The ears may be set low and posteriorly rotated. There may be a high arched palate. Often there is a short neck and widely spaced nipples. Scoliosis and vertebral anomalies are often found.

In males, abnormal genitalia including a small penis and scrotum and cryptorchidism, seem to be the rule. Flexion contractures of all fingers are common. Abnormalities of the toes as well as clubfeet and "rocker bottom" feet have been described.

Some patients have seizures. There is an increased incidence of infection in infancy, but these patients appear to have a relatively normal life expectancy. This syndrome can be diagnosed prenatally through amniocentesis, which should be offered to all individuals with previously affected children.

Turner syndrome. In 1938, Turner described females with sexual infantilism, short stature, and webbing of the neck. This phenotype was consistent with the chromosomal karyotype of 45,X discovered by Ford in 1959. Since then the name "Turner syndrome" has been applied to many females with ovarian dysgenesis and short stature, but only about 60% of them have a 45,X karyotype (Figure 21, p. 39). The remainder have various structural abnormalities of an X chromosome or mosaicisms such as 45,X/46,XX. The 45,X phenotype is the best described. The incidence of this abnormality is approximately 1 in 2,500 live female births, but the vast majority of conceptuses with Turner syndrome are spontaneously aborted.

Patients may be recognized at birth, the most common findings being slightly shorter than average length and congenital lymphedema, which usually involves the feet and lower extremities but may involve the arms, hands, and neck as well. These infants often have a very short neck with redundant skin folds at the back. Other observations include cup-shaped ears with fleshy auricles; a shield-shaped chest with widely spaced nipples; cardiovascular malformations, such as coarctation of the aorta or aortic valve malformation; urinary tract malformations such as horseshoe kidneys; and short metacarpals. With increasing age, short stature becomes more pronounced.

Toward puberty these girls fail to develop secondary sex characteristics and usually have amenorrhea. In most cases a laparoscopy reveals replacement of ovaries by fibrous streaks, which are responsible for the primary amenorrhea. All girls with Turner phenotype are not necessarily sterile, but infertility is certainly one of its most prominent features. The overwhelming majority of girls with Turner syndrome are of normal intelligence but may have some spatial perceptual problems as well as hearing impairment.

Since congenital lymphedema is the hallmark of the newborn but does not have to be present, suspicion of Turner syndrome may depend upon short stature (Figure 22 a, b, p.40). It is important to make the diagnosis of Turner syndrome as early as possible since the psychologic impact of this particular syndrome may be significant. Not only are these little girls short, but at puberty their failure to develop secondary sex characteristics may be devastating. Early diagnosis can certainly lead to treatment to promote sexual development. Sterility, which is present in most cases, will handicap them as they grow older, however.

The recurrence risk in Turner syndrome is not increased and the diagnosis can be made prenatally by amniocentesis and fetal amniocyte culturing.

Klinefelter syndrome. This syndrome was first described by Klinefelter in 1942. It was then shown in 1959 by Jacobs and Strong to be due to a chromosomal abnormality, usually a 47,XXY karyotype. The overall incidence of this sex chromosome abnormality is approximately 1 in 1,000 live male births and is associated with increased maternal age. Klinefelter syndrome cannot be diagnosed in the neonatal period nor during infancy since there is no distinct phenotype. The karyotype of 47,XXY may be found during screening of a newborn population, but the most common time of diagnosis is at puberty when the boy might present with gynecomastia. Other features that may be found at that time are small testes, rather scant facial and chest hair, abnormal pubic hair distribution, a eunuchoid body build, and often an above average height with very long limbs. Also found are infertility due to hyalinization of seminiferous tubules and impaired spermiogenesis.

These young men very frequently have significant personality deviations. A small percentage are mentally retarded. Since there is no associated phenotype, Klinefelter syndrome may escape detection after the age of puberty, and it is estimated that 10% to 20% of all men with Klinefelter syndrome are first diagnosed in infertility clinics.

Klinefelter syndrome can be partially treated, particularly if it is detected just before puberty because testerone treatment may help these boys undergo pubertal changes at the same time as their peers. Because of personality deviation and maladjustments, psychotherapy may also be helpful.

There is no significant recurrence risk for Klinefelter syndrome and cytogenetic diagnosis can be made prenatally.

The XYY syndrome. The XYY karyotype was first described by Sandberg in 1961, but it was not until 1965 that Jacobs suggested that the presence of two Y chromosomes may predispose to abnormally aggressive behavior. It is now evident that this cannot be proved.

Overall, 1 in 1,000 male births results in an XYY karyotype, an incidence discovered in surveys of large newborn populations. It has become increasingly apparent that, despite earlier implications, there is no specific phenotype associated with the XYY karyotype.

Psychosocial problems may play a role, but it seems that the vast majority of XYY men function quite normally and are never detected. It is well documented, however, that the XYY genotype occurs more frequently in institutions for the mentally retarded or socially delinquent. A definite relationship between this genotype and emotional or criminal behavior has yet to be established. At present, the XYY syndrome is more aptly named the "XYY karyotype."

In most cases, it is a finding of population surveys and not associated with any specific physical abnormalities. The importance of finding an XYY karyotype in a given man is being widely disputed because no consensus exists about informing families and patients of possible consequences, which remain conjectural.

Chapter 5

Environmental Agents

Two recent review articles by Kalter and Warkany provide a valuable introduction to the environmental causes of birth defects. It has been estimated that 3% to 10% of all such defects may be caused by known environmental factors. Approximately 25% of birth defects are due to primary genetic or chromosomal problems, while the causes of the remaining 60% to 65% are still unknown.

Interest in environmental agents as a possible cause of birth defects arose from the known malformations resulting from maternal rubella infections. Thalidomide-induced malformations in the early 1960s also focused attention on the teratogenic effects of drugs.

A teratogenic agent or teratogen acts during pregnancy to produce a physical or functional defect in the conceptus. Most teratogens are considered mutagenic agents as well. A mutagen is defined as an agent capable of causing a change in genetic material that can be inherited.

Interest in environmental agents as a possible cause of birth defects has risen steadily and efforts are increasingly made to identify and characterize them. It is extremely difficult to prove a causal relationship, however.

It is always very difficult to extrapolate from animal experiments to humans. Furthermore, different animal species react differently to environmental exposures. If a certain defect is found in only one animal species, it may not indicate any difficulty for humans at all. If a number of species show similar effects from an environmental cause, the results have greater significance in predicting human responses.

The developmental stage of the conceptus at the time of the exposure is also very important. Certainly, the most sensitive embryonic period is that of organogenesis, which occurs early in pregnancy. Gestational days 20 to 40 are often called the "window of vulnerability."

Specific agents act in specific ways to cause abnormal development, and the nature of an agent determines its access to the developing tissues of the conceptus. The placental barrier differs from species to species and is the most critical factor in this regard. The dose of teratogen is important, as is the extent of exposure to other known or unknown environmental influences. To prove an agent's teratogenicity conclusively, its effect has to be reproducible. Teratogenicity studies cannot be performed on humans and it is usually necessary to depend on animal studies.

Animal experiments yield suggestive, though never conclusive, results as to an agent's teratogenic properties in humans.

The effects of environmental factors on humans must usually be determined through epidemiologic studies, but such research is subject to many errors. When humans take drugs it is usually for a specific reason, most often an underlying disease. The disease and not the agent

may cause an observable birth defect, and often the drug cannot be specifically implicated. Other confounding factors are more difficult to recognize and may escape notice altogether. Also, epidemiologic studies easily become biased. Proper design and statistical methods of evaluation prevent or correct much of the bias but sometimes does not eliminate it entirely. The occurrence of birth defects may also be a chance association with the intake of drugs or other agents thought to be teratogenic. Adequate numbers of cases must be recorded and analyzed for statistical significance before firm conclusions can be drawn.

Concern about a substance's teratogenicity is only one aspect of the problem. Humans are exposed to agents at work or in the environment that may damage them in other ways.

Chemical mutagens are certainly monitored carefully but, at present, the only practical method of screening human populations for genetic damage may be cytogenetic monitoring. But, cytogenetic monitoring has been found to produce quantitative results only with respect to exposure to ionizing radiation; it does not yield reliable data after exposure to ionizing chemicals. Furthermore, abnormal findings, such as sister chromatid exchanges, may not be relevant unless chromosome analysis of exposed individuals is performed before exposure as well so that a change may be observed. Other methods of monitoring have been proposed but none is reliable or practical. Future biologic monitoring may include cytogenetic analysis, microbiologic mutagenicity assays, and detection of DNA adducts in biologic fluids. The field needs further investigation as part of preventive medicine and occupational health.

Teratogenic agents are of consequence because of maternal exposure to them. The exposure of fathers to teratogens is of no significance unless the agent also has a mutagenic effect.

Specific teratogenic effects seem to be proven for some environmental agents (Table, p. 43). It appears that ionizing radiation may cause birth defects largely involving the central nervous system if the pregnant mother has been exposed to 5 rads or more; no damage has been found after lesser exposures. Heavier radiation usually results in abortion, but infants may be born with microcephaly and other central nervous system defects.

Among chemicals that cause damage, methyl mercury or organic mercury seems to be associated with specific abnormalities. This has been reported mostly in Japan and other areas outside the United States. The abnormality caused by methyl mercury poisoning, Minimata disease, followed the eating of contaminated fish and revealed neurologic damage secondary to disturbed brain development. Other agents including hexachlorophene, spray adhesives, chemical wastes, and lead are suspected of causing specific damage, but this is not proved.

Special attention has been given recently to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and to dioxin, also called 2,3,7,8-tetrachlorodibenzo- *p* -dioxin or TCDD. 2,4,5-T is an herbicide and was a component of Agent Orange. Dioxin is a contaminant of this once widely used herbicide, now banned in the United States. Both 2,4,5-T and TCDD are teratogens, but only in rodents and only when the rodents are given far larger doses relative to their weight than humans have probably ever been exposed to. At this point, neither has been proved to be teratogenic in humans.

Drugs that have caused problems in humans are thalidomide, which causes the well-known defect phocomelia; steroids that may masculinize the female fetus; and cytotoxic drugs such as folic acid antagonists, which chiefly cause miscarriages but have produced a 20% to 30% incidence of malformations in babies. Tetracycline has been implicated as a cause of dental staining in fetuses.

Among all the addictive drugs, including LSD, marijuana, cocaine, phencyclidine, amphetamines, heroin, and methadone, only the last two have been found to be associated with an increased rate of stillbirths, reduced birth weight, and neonatal withdrawal symptoms. No consistent malformations have been found in children born to mothers who use any of them.

It is well known that infectious agents can cause congenital malformations. The documented infectious agents resulting in fetal malformations are rubella, cytomegalovirus, and toxoplasma gondii. Suspected agents include herpesvirus II, coxsackievirus B, treponema pallidum, and varicella. Overall, it seems that infectious agents play a major role and are more important than chemicals or drugs in teratogenesis. It is estimated that approximately 2% of all congenital malformations are the result of infectious agents.

Although very few environmental agents can be clearly implicated as a cause of consistent malformation syndromes, some strong associations do exist. Two examples are presented. *Fetal alcohol syndrome* occurs regularly as a result of a pregnant woman's chronic alcohol intake. The incidence has been estimated to be as high as 1 in 1,000 live births. Heavy alcohol intake, particularly during the first trimester, may cause significant malformations since alcohol readily crosses the placenta. The clinical findings in the infant may result from toxicity of the alcohol itself or a metabolic breakdown product of the alcohol. There certainly seems to be a consistent effect if the mother has taken at least four drinks per day. No major fetal effects have been noted when the mother's intake is less.

Fetal alcohol syndrome does not occur regularly in all offspring of chronic alcoholic mothers; it is seen in 30% to 50% of the offspring. Some of the syndrome's clinical features are pre- and postnatal growth deficiency, dysmorphic features including short palpebral fissures, epicanthal folds, ptosis, a smooth philtrum, midfacial hypoplasia, and microcephaly. Central nervous dysfunctions such as mental retardation, hyperactivity, and learning and behavioral disorders also occur with increased frequency. Although chronic alcoholism probably results in damage to the fetus in a significant number of cases, the real cause of fetal alcohol syndrome has not been elucidated.

Another example of a drug's teratogenic effects is the *fetal hydantoin syndrome.* Ten percent of the offspring of mothers who have to take hydantoin during pregnancy, may have serious malformations, while 30% have minor ones. Hydantoin readily crosses the placenta, but it is not quite clear whether the agent itself or a metabolic product causes the defects and problems seen in children with the syndrome.

Some of the clinical features of the syndrome are mild growth and brain growth deficiency. The latter may be associated with mental retardation, behavioral disorders and microcephaly. A short nose with anteverted nostrils and a low bridge, a long philtrum, and small distal digits with small nails have been reported. All these defects have been found with increased frequency. It has also been documented, however, that the incidence of major malformations, especially defects such as cleft lip, and cleft palate, and congenital heart disease, occur with an increased frequency in children of untreated epileptic mothers. It is therefore thought that the mild dysmorphic features may represent fetal hydantoin syndrome and that anticonvulsants are probably not the only cause of some of the other major malformations.

Figure 3. Patient with Waardenburg syndrome

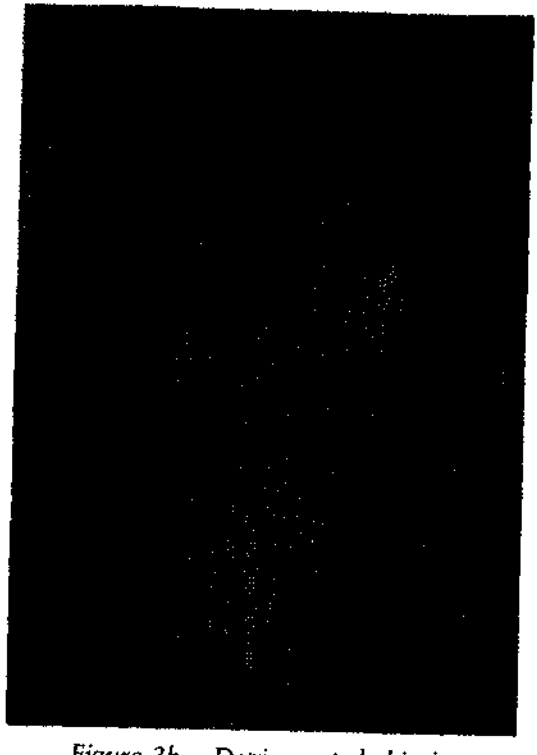

Figure 3b. Depigmented skin in Waardenburg syndrome

Figure 4a. Patient with Marfan syndrome

Figure 4b. Arachnodactyly in Marfan syndrome

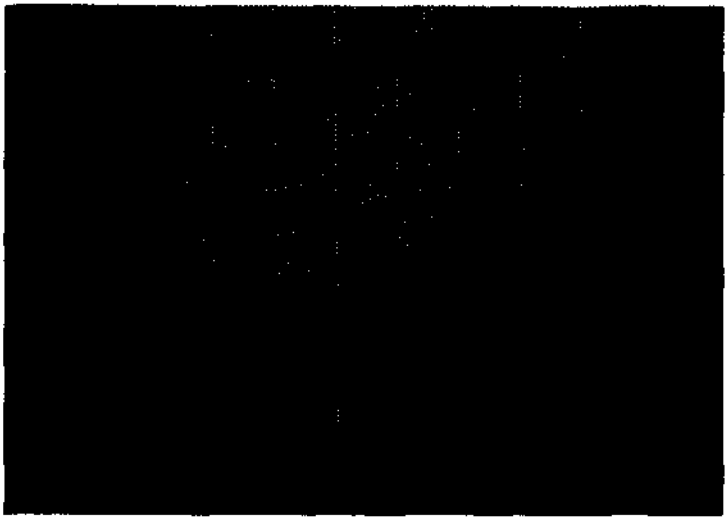

Figure 5. Cafe-au-lait spot in neurofibromatosis

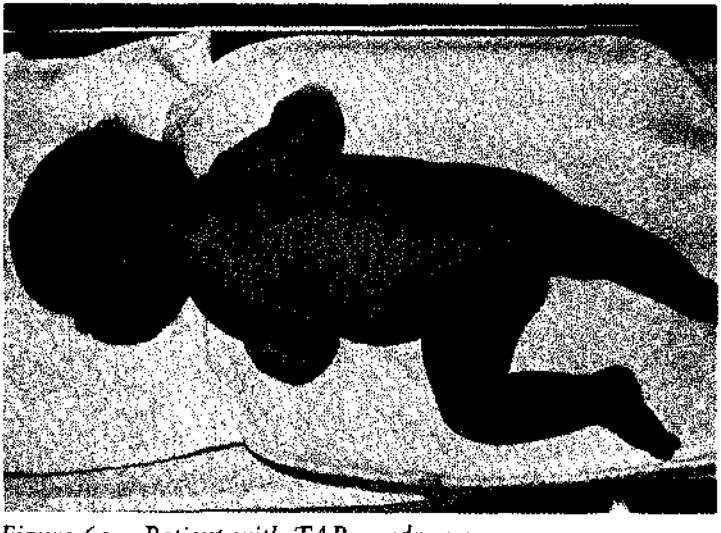

Figure 6a. Patient with TAR syndrome

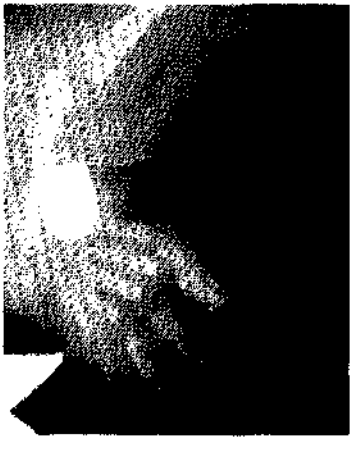

Figure 6b. Absent radius in the TAR syndrome

Figure 7a. Patient with Hurler syndrome

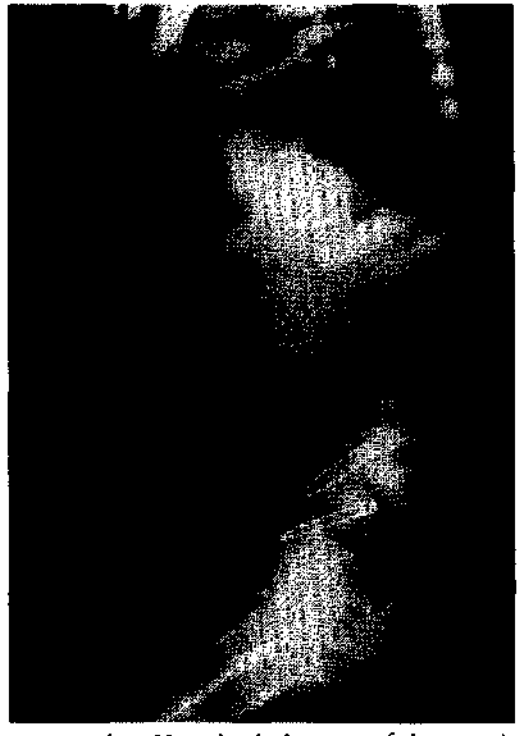

Figure 7b. Vertebral changes of dysostosis multiplex in Hurler syndrome

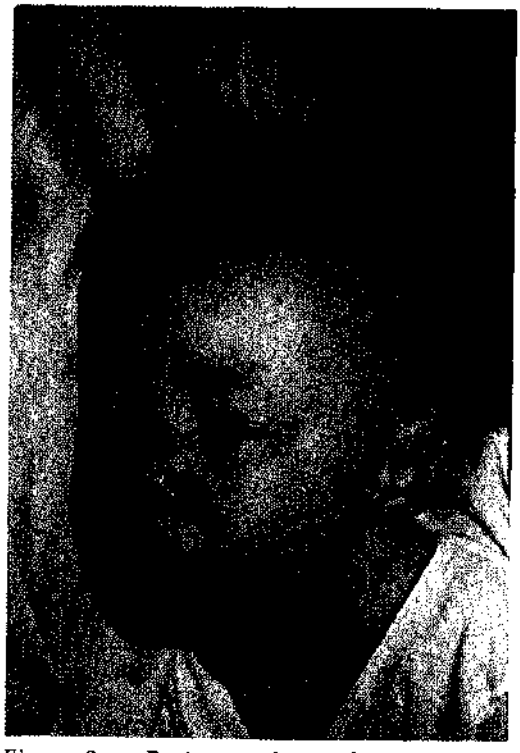

Figure 9a. Patient with Menkes syndrome

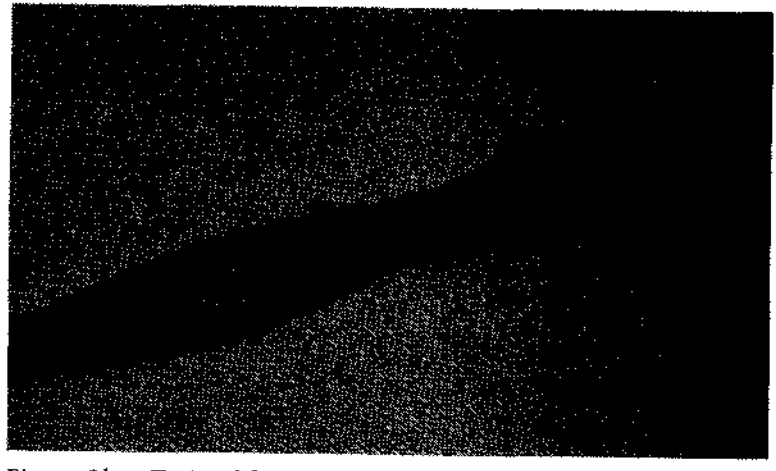

Figure 9b. Twisted hair as seen in Menkes syndrome

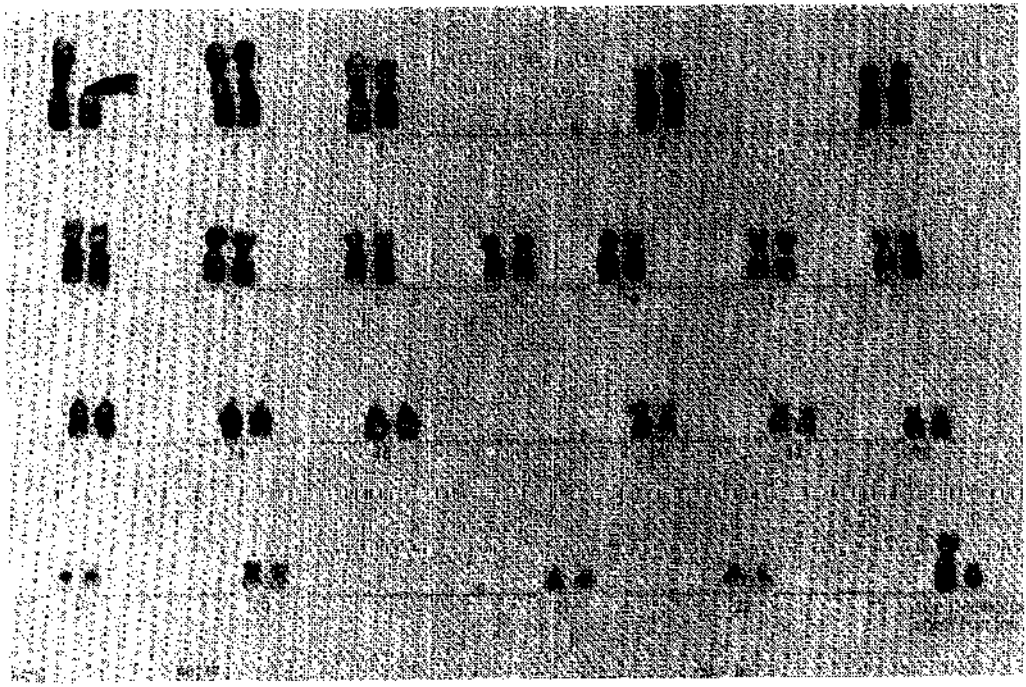

Figure 12a. Normal male karyotype - C-banding

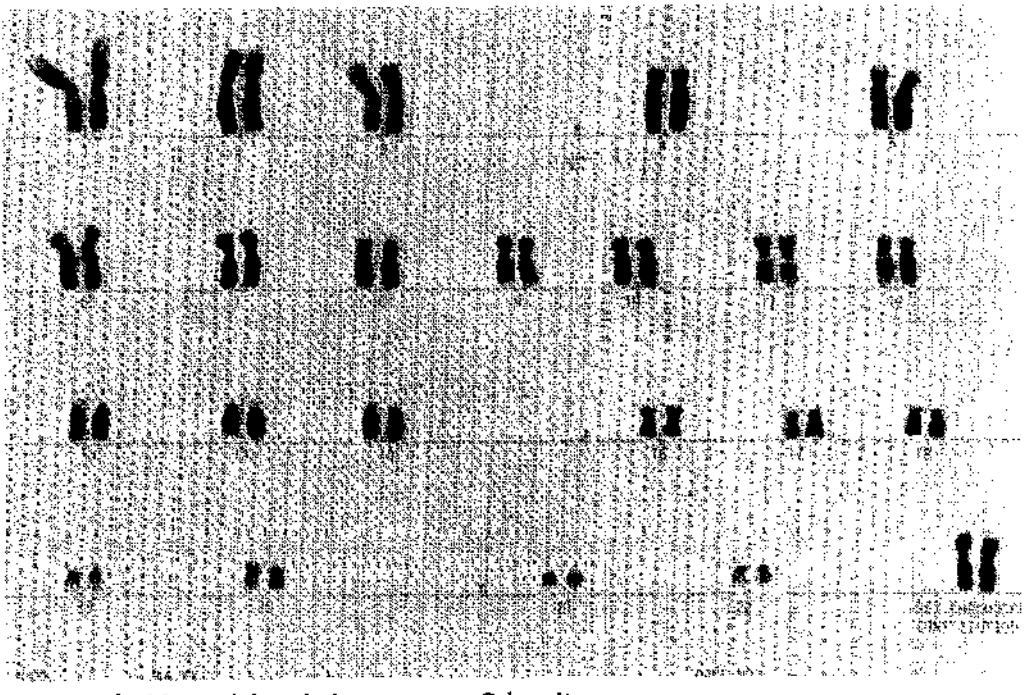

Figure 12b. Normal female karyotype - C-banding

Figure 14. Patient with Down syndrome

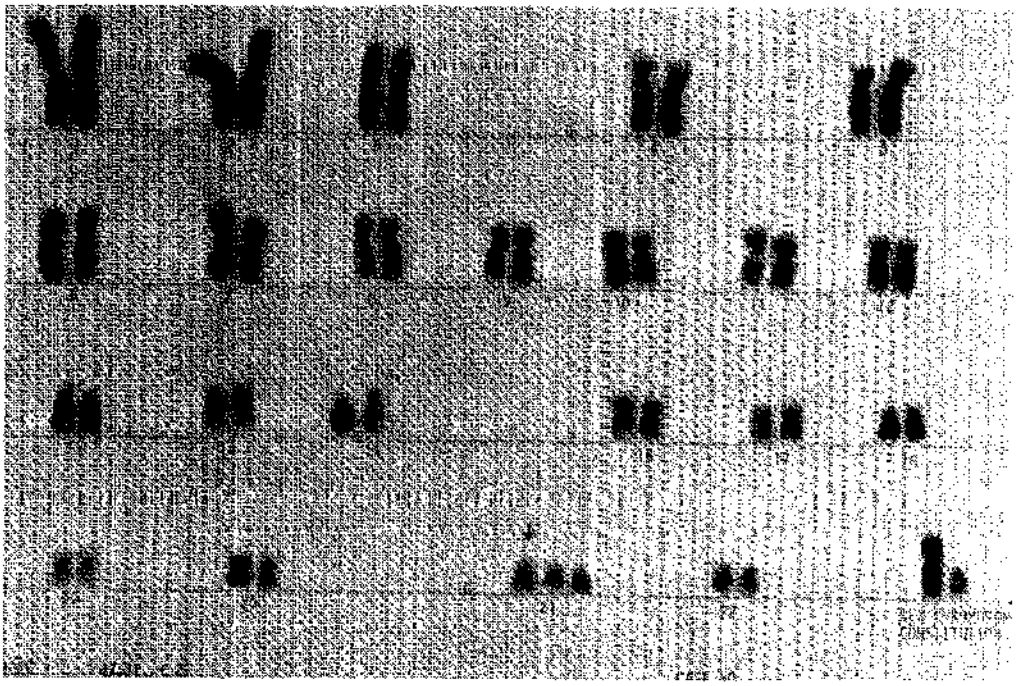

Figure 15. Trisomy 21 karyotype

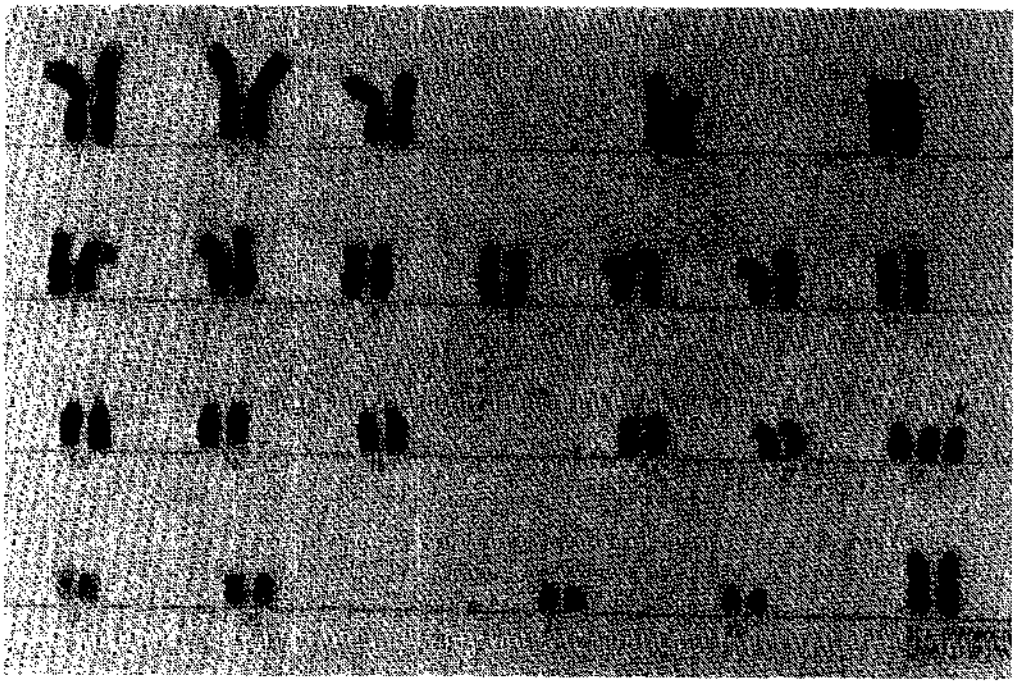

Figure 16. Trisomy 18 karyotype

Figrue 17. Patient with trisomy 18

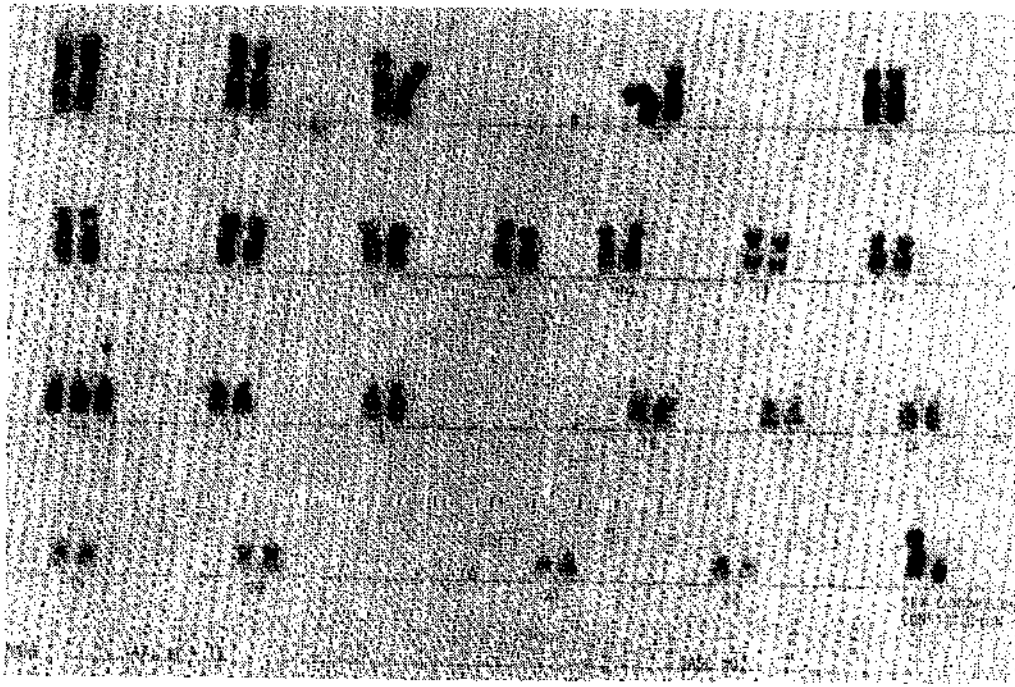

Figure 18. Trisomy 13 karyotype

Figure 19a. Patient with trisomy 13

Figure 19b. Scalp defect in trisomy 13

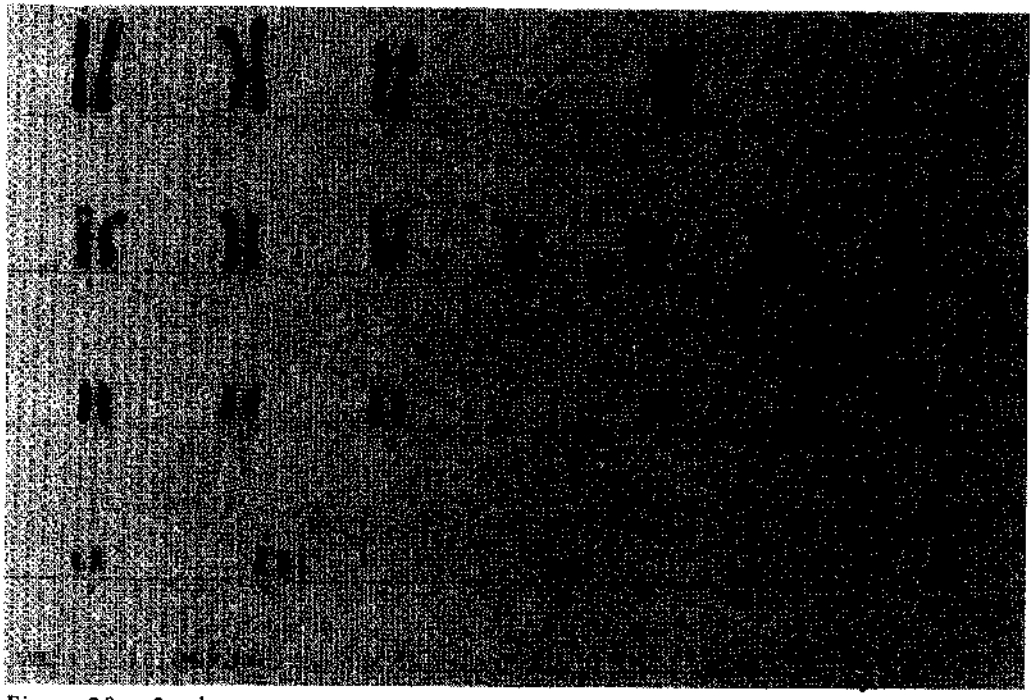

Figure 20. 5p- karyotype

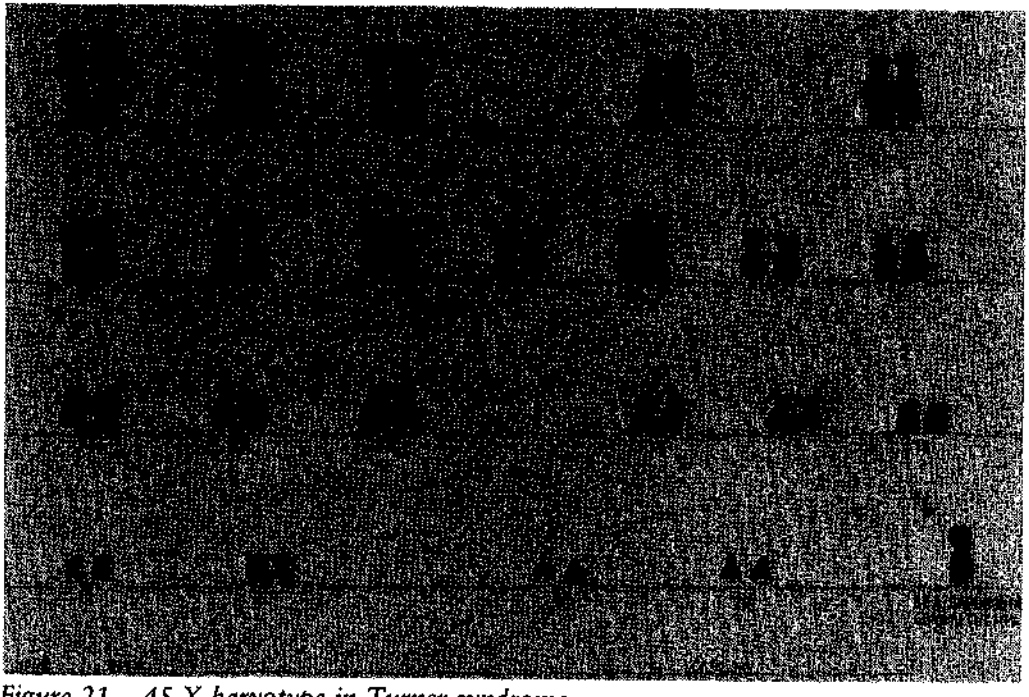

Figure 21. 45,X karyotype in Turner syndrome

Figure 22a. Patient with Turner syndrome

Figure 22b. Patient with Turner syndrome

Chapter 6

Genetic Counseling

Genetic counseling should form part of every evaluation of birth defects and of family planning in families with known genetic problems. Not everyone may benefit from counseling. A young couple who plan to marry, who have no evident defects in either of their families, and who do not belong to any population group at risk will learn only that the risk of a birth defect occurring in their child will be the same as that of the general population, about 3%.

What, then, is genetic counseling? It is assessing the risk of having a child with a genetic defect and the risk of a recurrence if the child has a hereditary problem. Genetic counseling has many other components in addition.

Who should have genetic counseling? Couples who might benefit from it are those: (1) who know of a hereditary disease in their families; (2) in which one or both spouses is known to suffer from a genetic defect; (3) who have been found through screening procedures to be carriers of a specific genetic trait; (4) who has had a child with a recognized genetic defect or a chromosome disorder; or (5) in which the wife has had several miscarriages without an identified medical cause.

What are the prerequisites for genetic counseling? First and foremost is a correct diagnosis. If a couple is referred because its child has a potential genetic problem, the counselor must pursue a proper diagnosis. This may involve an extensive workup, including such studies as chromosome analysis, enzyme assays, diagnostic x-rays, and possibly various consultations with specialists. Proper diagnosis also means obtaining a complete family pedigree of at least three generations. The counselor must be prepared to discuss the situation based on knowledge of the condition. Preparation may be time consuming, but is absolutely essential.

As important as knowledge of the disorder is an understanding of its genetics. Such hereditary diseases as Charcot-Marie-Tooth disease (peroneal muscular atrophy) are known to be inherited as an autosomal dominant, autosomal recessive, and as an X-linked disorder. Other birth defects may be multifactorial in origin, but it must not be overlooked that some conditions may be part of a syndrome known to be inherited as a Mendelian disorder.

When a proper diagnosis has been established and the counselor has the necessary information, the genetic counseling session should usually include both parents. Often the first question by the parents of an affected child is, "What are our chances that this can happen again?" Other factors have to be considered as well before a decision regarding a future pregnancy can be made.

Included in the discussion should be the disorder itself. What is the long-term outlook? Will the affected child have a significant socioeconomic impact on the family? Will the condition get worse or is it stable? The answers to these questions may have as much influence on family planning as genetic risks.

Another important aspect to be discussed includes prenatal diagnosis. Techniques for such diagnosis have improved rapidly and a number of hereditary conditions can now be determined before birth. Most of the techniques include amniocentesis and analysis of cultured fetal amniocytes, but ultrasound has also been an important adjunct to prenatal diagnosis. Prenatal diagnosis often requires moral and ethical decisions from a couple, but its availability should always be mentioned. If prenatal diagnosis is discussed in a counseling session, it is of utmost importance that the counselor be aware of existing facilities to help with proper referrals.

One of the most important aspects of genetic counseling is obviously the delineation of the genetic occurrence and recurrence risks. Some of the more common referrals for counseling will involve couples who have had a child with a chromosome disorder such as Down syndrome.

If Down syndrome has been diagnosed as due to trisomy 21, the family must be informed that the recurrence risk is negligible under the maternal age of 35 years. After that the risks increase with advancing maternal age. But if the syndrome is due to a 13/21 translocation for example, and if one of the parents has been identified as a balanced translocation carrier, the risks are greatly increased over those for Down syndrome due to trisomy 21. If a mother has been found to be a 21/21 translocation carrier, however, she will have only children with Down syndrome. Specific risk figures for most of the recognized chromosomal disorders are available and should be cited in genetic counseling sessions. Furthermore, it should be mentioned that cytogenetic disorders can be diagnosed prenatally.

If *single gene* disorders are involved, it is important that the couple have a proper understanding of the genetics. A recurrence risk of 25% for each pregnancy, after an *autosomal recessive disorder* has been identified, means that the risk remains the same for each subsequent pregnancy. It is not true that after one affected child representing the 1 in 4 chance has been born that the next three children will be unaffected. The 25% risk is true for each pregnancy.

A person affected by an *autosomal dominant trait* needs to know that the chance of having an affected child is 50% with each pregnancy. The 50% figure might be readily understood, but other factors such as knowledge of intrafamilial variations and severity of the defect may play a deciding role.

Counseling for multifactorial disorders is especially important. The recurrence risks applicable after one affected individual has been identified are often on the order of 3%, but this has to be considered in light of the incidence of a specific defect in the general population. It is also important in counseling on multifactorial defects that the parents are made aware that with each additional affected child the risks increase.

Since genetic counseling sessions are often emotional experiences for the people involved, it is important to reinforce counseling over time. This may be done through repeated sessions, followup visits with professionals trained in genetic counseling, or a letter summarizing counseling sessions. It is also most important to assure the family of the availability of

repeated access to the genetic counselor. The family should be assured that the genetic counselor will support them regardless of what decision they make after the counseling session.

Some examples of incidence and recurrence risks for multifactorial disorders are given in the following Table:

Recurrence risk for multifactorial disorders

Disorder	Incidence per 1,000 newborns	Recurrence risk (%) after one affected child	Recurrence risk (%) after two affected children
Isolated cleft lip with or without cleft palate (CL/CP)	1-2	4	12
Congenital heart disease	5-7	2-4	5-8
Neural tube defect (anencephaly, myelomeningocele)	1.5-2	4	10

Chapter 7

Screening

Screening has become a matter of everyday life in our society. Some screening is conducted all the time. Job applicants are screened; students are screened in school, not only for intellectual ability and proper placement but routinely for vision and hearing in many school systems.

Screening should also play a significant role in health care and preventive medicine. Screening in medicine, however, has not yet reached perfection.

Many states have enacted laws requiring newborn screening. Although such screening works reasonably well in most states, some imperfections are present in all systems. Babies born at home may be missed, as may those who are discharged shortly after delivery before there is an opportunity to do the screening procedure. Even when a blood sample has been obtained, accurate testing must be completed and the results must reach the physician in charge of the patient. Each step provides a potential for error.

Furthermore, in newborn screening the educational aspects of state laws have been neglected. The physician may not know what kinds of screens are performed at the state level or what a positive screening test means. Parents will frequently ask if their baby has been screened and if so for what diseases. It is important that the information be available in hospitals or as educational materials so that no misconceptions arise.

Only a few diseases are routinely screened for in the newborn period, and it is important to realize that positive or negative results for the few do not always provide a correct or complete answer. All tests are expected to be specific and sensitive enough to give only a minimal number of false-negative and false-positive results. A false-negative should never be taken as accurate if there are clinical signs and symptoms of a problem that suggest the disease for which the baby has been screened. It is also as important to realize that a positive screening test does not produce a definitive diagnosis; further confirmatory studies are always necessary. If screening is required by law and is not performed, a malpractice suit may result. This certainly can be avoided.

The most important objective of screening the newborn, of course, includes the prevention or minimization of damage and the avoidance of delay in diagnosis. Newborn screening can also include education of the parents and the public as well as specific counseling on recurrence risks.

The most commonly cited example of the benefit of newborn screening is *phenylketonuria*. Early detection of this autosomal recessive disease is important for two reasons. First, an affected baby can lead a reasonably normal life if the diagnosis is made early and proper treatment instituted. Second, the family can be made aware that each subsequent pregnancy carries a 25% recurrence risk.

Other examples in which newborn screening uncovers conditions that are amenable to treatment and improves the quality of life are *galactosemia* and *homocystinuria*. Early screening helps in the management of some illnesses that have no cure but can be managed symptomatically. Examples are cystic fibrosis, sickle cell anemia, and thalassemia. Neonatal screening for glucose-6-phosphate-dehydrogenase deficiency may also be important since exposure to certain agents and drugs may cause significant hemolytic disease in the affected individual.

It is relatively easy to perform screening in the neonate, find the affected, and refer the family for genetic counseling. It is generally expected that this will be done and that proper genetic counseling will be provided so that a couple can make a more intelligent decision about their reproductive future.

Newborn screening enacted into laws has been widely accepted by the general public, but screening should not be confined to the newborn. It might be advisable at times to continue screening persons with syndromes which have a predilection for malignancy, such as multiple endocrine adenomatosis or the basal cell nevus syndrome. Early detection of a malignancy improves life expectancy and quality.

It is also expected that certain well-defined populations, such as individuals who are handicapped and confined in institutions, may be screened prospectively. It is known that a significant number of institutionalized people will have genetic diseases that should be identified.

A more significant problem arises when screening entire populations is advocated. This can be done successfully in certain ethnic groups which have defined, increased risks for genetic diseases. An example might be Ashkenazi Jews who have a significantly higher than usual carrier rate of Tay-Sachs disease. Other far-reaching population screening programs have been fraught with some difficulties, because the information obtained has occasionally been misused and education and counseling have sometimes been lacking. Large-scale screening of certain population groups can therefore be considered only when certain criteria have been met. These include the facts that screening offers a general public benefit, appropriate educational facilities are available, laboratory facilities, reporting procedures, and test methods are satisfactory, and proper counseling and education are implemented.

In short, screening should be performed only if the benefits outweigh the costs to society. Because of these requirements and some reported abuse, the National Genetic Disease Act now requires that parents' representatives be included in the decision-making process.

Genetic screening is an important tool which should be a part of preventive medicine. If procedures are applied properly and adequate educational materials and counseling are provided, screening can be advocated. In any event, screening procedures should always result in benefits to the patients and their families.

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GLOSSARY

Acrocentric: Refers to the centromere being located near the end of the chromosome.

Allele: Alternative genes that occur at the same locus on homologous chromosomes.

Amniocentesis: The process of obtaining amniotic fluid from the pregnant uterus. Useful in prenatal diagnosis.

Anomaly: An abnormality; often a birth defect.

Autosome: Any non-sex chromosome. Includes pairs 1 through 22.

Banding: The property of chromosomes to take up specific stains in specific DNA regions producing a banded appearance.

Barr body: The condensed inactive X chromosome represented as a dense sex chromatin mass in the periphery of a somatic cell.

Carrier state: Refers to individuals known to carry a recessive abnormal gene in a single dose and without phenotype expression. Also refers to balanced chromosomal rearrangement.

Chromosome: An intracellular structure bearing genes.

Congenital: Present at birth.

Consanguinity: Refers to relationship between blood relatives, i.e., consanguinous mating causing potential increased risk for offspring.

DNA: Deoxyribonucleic acid. The nucleic acid of the chromosomes which carries the genetic code.

Deformation: Refers to structural deviations of body parts representing an abnormal position.

Deletion: Most commonly used to denote loss of a portion of a chromosome.

Diploid: The number of chromosomes in most somatic cells in humans, N = 46.

Dominant: Most commonly used to refer to a trait that is expressed in the heterozygous state. A single abnormal gene is expressed as an abnormality.

Duplication: Presence of part of a chromosome in duplicate.

Dysmorphology: The study of morphological abnormalities as seen in syndromes of malformations.

Ethnicity: Relates to the increased frequency of genetic traits in certain ethnic populations.

Familial: Characteristics present in more than one member of a family. Includes multifactorial traits.

Fetoscopy: A technique used for direct visualization of the fetus.

Gene: The smallest functional unit of heritable transmission. A segment of a chromosome (usually a segment of DNA) with detectable functions.

Genotype: The genetic constitution of an individual. Most commonly used for alleles present at one locus.

Haploid: The chromosome number of a normal gamete (N = 23 in humans). Includes one chromosome of each type.

Hereditary: Refers to genetic traits which have the potential to be transmitted to the next generation.

Heterozygote: A carrier of different alleles at a given locus on homologous chromosomes.

Homologous: Refers to a pair of chromosomes having the same gene loci in the same order. One chromosome from each parent.

Homozygote: Having the same allele at a given locus on homologous chromosomes.

Incidence: The relative frequency of a trait or disease at birth.

Karyotype: A set of chromosomes of a single cell arranged in a standardized fashion.

Linkage: Describes the proximity of genes at loci which may be so physically close as to be inherited together.

Locus: Position of gene on a chromosome.

Malformation: A structural abnormality of an anatomic part.

Mendel, Gregor: Austrian monk. Originator of "Mendelian Genetics."

Mendelian: Refers to single gene determined traits that segregate in families.

Metacentric: A chromosome with centromere at or near the middle of the chromosome.

Mitosis: Somatic cell division resulting in the formation of two cells, each with the same chromosome complement as the parent cell.

Monosomy: The condition in which one chromosome of a pair is missing. Example: 45,X Turner syndrome is a monosomy of the X chromosome.

Monozygous: Refers to twins who arise from a single zygote.

Mosaicism: The presence in a single individual of at least two different cell lines containing different genetic make-ups.

Multifactorial: A trait whose expression is under the control of both genetic and environmental factors.

Mutation: A permanent heritable change in the genetic material.

Occurrence risk: The incidence of a specific trait or disease in a defined population.

p: The short arm of a chromosome.

Phenotype: The observable physical and biochemical nature of a person without regard to causation.

Polygenic: Determination by many genes at different loci with small additive effects.

Prenatal diagnosis: Determination of the status of well-being of a fetus before birth using varying techniques.

Proband: The affected person who first draws attention of a geneticist in a given pedigree.

q: The long arm of a chromosome.

Recessive: A trait that is expressed as a phenotypic abnormality in the homozygous state only.

Recurrence risk: Determines the probability that a certain disorder in a person will recur in a family in the same or subsequent generations.

Sex chromosome: The X and Y chromosomes.

Sex linked: X-linked. Refers to gene(s) located on an X chromosome.

Siblings: Brothers and sisters (of an index case).

Sporadic: A trait that occurs in a member of any family but carries no increased probability of occurring in a second family member.

Syndrome: A set of signs and symptoms that occur together.

Teratogen: An environmental agent that produces or raises the incidence of congenital malformations.

Translocation: The transfer of a whole or part of a chromosome onto another chromosome resulting in a compound chromosome containing parts of the original ones.

Trisomy: Three chromosomes of one type in a person. Example: 3 number 21 chromosomes in Down syndrome due to trisomy 21.

X-linked: Traits determined by genes on the X chromosomes.

Zygote: The diploid single cell formed by the union of a haploid ovum and a haploid sperm.

CASE-CONTROL STUDY OF CONGENITAL ANOMALIES AND VIETNAM SERVICE
(Birth Defects Study)

REPORT
TO THE MINISTER FOR VETERAN'S AFFAIRS
JANUARY 1983

AUSTRALIAN GOVERNMENT PUBLISHING SERVICE
Canberra 1983

SUMMARY

This investigation was originally designed and commenced by Dr. Robert MacLennan, then Associate Professor of Epidemiology, Commonwealth Institute of Health, University of Sydney, and continued by Dr. John Donovan, the Senior Adviser in Epidemiology to the Department of Health. Dr. Donovan later modified certain aspects of the original design in the light of the field experiences of his team and was responsible for conduct of the Study and preparation of this Report.

The investigation involved examination of the hospital and cytogenetic laboratory records of infants born with anomalies (birth defects) in New South Wales, Victoria and the Austrailian Capital Territory between the years 1966 and 1979 inclusive. In all, 34 hospitals and 4 cytogenetic laboratories were involved and co-operated fully with the investigating team. Whenever the birth of an infant with an anomaly was detected, it was matched to a healthy control infant born in the same hospital, to a mother of similar age, and as close as possible in time to the birth of the child with the anomaly.

The fathers of both cases and controls were indicated in 8,517 instances and those identified were compared with a list of every man who served in the Australian Army between 1962 and 1972, which was the period of Australian involvement in Vietnam. Fathers identified as having served in the Army during this period were then classified according to whether or not they had served in Vietnam. The sample was large enough to enable the study to meet its aims.

The important finding from the study is that 127 of the fathers of children with anomalies were Vietnam veterans, whilst 123 veterans were amongst the fathers of healthy children. This indicates that there is no evidence that Army service in Vietnam relates to the risk of fathering a child with an anomaly.

The finding given above needs to be confirmed by statistical analyses. These use the most appropriate and up-to-date methods.

The first statistical examination confirms that the matching of malformed with healthy infants was generally adequate, but that a small additional statistical adjustment for age of mother may be necessary in later analyses. Risk was least for mothers aged 25.

Other factors on which information was available and which might bear on risk were then examined. The risk of malformation is higher in male children than in female, and in multiple than in single births. The nature of both these relationships also varies with age of the mother. Statistical techniques were used to allow for these relationships in later analyses of risk associated with Vietnam service of the father. Another factor examined which needed to be taken into account in these later analyses was birthplace of the father. Factors examined which proved not to need to be taken into account included age of the father, socio-economic group of the father, birthplace of the mother, and urban or rural residence of the parents.

The study gives persuasive evidence that Vietnam service has not been associated with any important increase in the risk of birth defects in children of veterans. According to the stand-

ard statistical estimation procedure, there is a 95% chance that the true value of the risk of a Vietnam veteran fathering a malformed child compared with that of a non-veteran lies between 0.78 (a 22% decrease) and 1.32 (a 33% increase). The most likely estimate of the risk is 1.02, only 2% greater than no difference at all in risk.

When the risks were estimated separately for Australian Regular Army and for National Service veterans they were found to be similar. The same applied for comparisons of risk in contemporary members of the Australian Regular Army and National Servicemen who did not serve in Vietnam, compared with Australian fathers who did not serve in the Army.

Comparisons of risk were also made with other aspects of Vietnam service which might have been expected to bear on an increase in risk, had one been found. While there was a tendency toward lower risk for veterans with longer Vietnam service, no effect on risk of this, of time between deplanement and conception, or calendar year of Vietnam service, was demonstrated.

When veterans were sub-divided according to whether they had served in Vietnam before conception of the child, or only afterwards, it was found that the risks were similar, with estimates slightly higher for children conceived before the father had been to Vietnam.

Examination of the study procedures revealed some limitations in data sources and handling. The analyses were repeated in ways which demonstrated that these could not have influenced the conclusions. It was also shown that the way in which the statistical adjustments for variables associated with risk were made did not affect the conclusions.

To the extent that was possible in a study of this size, the data were examined to see whether there was any single malformation or group of malformations sufficiently strongly associated with Vietnam service to justify further examination. No further examination was warranted.

The limitations of the data sources and their handling were further evaluated. This evaluation included the reworking of the processing for a 2% sample of the data. It was concluded that there should be considerable confidence in the validity of the findings.

There is no evidence that Army service in Vietnam has increased the risk of the birth of a child with an anomaly.

VIETNAM VETERANS' RISKS FOR FATHERING BABIES WITH BIRTH DEFECTS

August 1984

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
Centers for Disease Control
Center for Environmental Health
Atlanta, GA 30333

SUMMARY

Vietnam veterans' risks for fathering babies born with major structural birth defects were assessed by using a case-control study design. Case group index babies were registered by the Centers for Disease Control's (CDC's) Metropolitan Atlanta Congenital Defects Program during the years 1968-1980. With data from multiple sources, this program ascertains live and stillborn babies with structural defects born to women who are residents of the five-county metropolitan Atlanta area. To be included in the registry, a baby's birth defects diagnosis must have been made during the first year of life and recorded in a hospital chart by a physician. Control group index babies—babies born without defects—were selected from amoung the 323,421 babies who were live born in the area to resident mothers during 1968 through 1980. The control group index babies were frequency matched to the case group index babies by race, year of birth, and hospital of birth ("sampling design variables"). The number of case group families eligible for the study was 7,133, as were 4,246 control group families.

Information about paternal military service in Vietnam was obtained during 1982 and 1983 through interviews with the index babies' parents; information about a wide variety of other factors that might be associated with the occurrence of defects was also gathered using a computer assisted telephone interviewing system. Interviewed Vietnam veteran fathers were asked if they felt that they had been exposed to Agent Orange while in Vietnam. In addition, they were given scores (ranging from 1 to 5) reflecting subjectively estimated opportunities for exposure to Agent Orange (that is, a score on the Agent Orange Exposure Opportunity Index). These scores were based on location in Vietnam, period of service, and occupational duties, and were given without knowledge of the fathers' case control group status. All men who had served in Vietnam were also asked if they had contacted malaria while there, and whether they had used malaria chemoprophylactic medicines.

Before parents could be interviewed, they had to be located. Because many of the index babies were born many years before the interviews were done, locating the parents was often difficult. In all, 4,929 case group mothers and 3,029 control group mothers completed interviews (70% participation rate). Fewer fathers were interviewed: 3,977 from the case group and 2,426 from the control group (56% participation rate). The participation rates were lower for "Other race" than for "White race" parents, particularly for fathers; this may somewhat limit our ability to generalize about the results of the study. The major reason for nonparticipation was inability to locate parents.

For the purposes of data analysis, the birth defects that affected the case group index babies were classified into 96 groups, including 1 group compromising all types of defects combined. For each of these 96 groups four hypotheses were tested: 1)Whether veterans (excluding Vietnam veterans) were at a different risk for fathering babies with defects than non-veterans. The purpose of this test was to decide if Vietnam veterans should be compared with all other factors, or only with veteran fathers for the remaining three hypotheses. 2) Whether Vietnam veterans were at a different risk for fathering babies with birth defects. This hypothesis was the major focus of this study. 3) Whether Vietnam veterans who received higher Agent Orange Exposure Opportunity Index scores were at a different risk than other men.

4) Whether Vietnam veterans who said they believed that they had been exposed to Agent Orange were at a different risk than other men.

Each of the hypotheses for each of the 96 defect groups was evaluated three times. First, the hypotheses were evaluated with only the potentially confounding sampling design variables being considered. At this stage of the analysis, the possibilities that the risks varied with the time of birth and with race were assessed. Second, the hypotheses were evaluated with the sampling design variables and four other potentially confounding covariables being considered. These four were 1) maternal age, 2) maternal education, 3) maternal alcohol consumption, and 4) birth defects in the first-degree relatives of the index babies. These four covariables were identified prior to data analysis as being particularly important. Third, the hypotheses were evaluated with 108 potentially confounding maternal and paternal covariables being considered. These covariables were considered singly, each along with the sampling design variables. The main analytical tool used was conditional logistic regression; the Mantel-Haenszel procedure was, however, used for some analyses.

Four hundred and twenty-eight fathers of case group index babies were (said by mothers to be) Vietnam veterans and 268 fathers of control group babies were Vietnam veterans; the non-Vietnam veteran case and control group fathers numbered 4,387 and 2,699, respectively. For the analysis that gave no consideration to potentially confounding variables (except for the sampling design variables), the logistic regression-derived odds ratio for all types of defects combined was 0.97 with 95% confidence limits of 0.83 to 1.14. This estimate provides no support to the notion that Vietnam veterans, in general, have been at an increased risk for fathering babies with birth defects than other men.

With few exceptions, the same type of finding applied to Vietnam veterans' risks for the remaining 95 defect groups. The same overall pattern also applied to the tests of hypotheses regarding the Agent Orange Exposure Opportunity Index and those regarding Vietnam veterans' self-reports of Agent Orange exposure. Three exceptions to this general pattern are noted below; those instances in which Vietnam veterans, or subsets of them, appear to have been at lower risk than other men are not presented here.

1) The estimated risks for fathering babies with spina bifida were higher for Vietnam veteran fathers who received the higher Agent Orange Exposure Opportunity Index scores. No similar association was found with the related defect, anencephalus.

2) Vietnam veterans who had higher Exposure Opportunity Index scores had higher estimated risks for fathering babies with cleft lip with or without cleft palate.

3) The estimated risks for fathering babies with defects classed in the group "Other Neoplasms" was higher for Vietnam veterans who had higher Exposure Opportunity Index scores. The neoplasms classified in this group include teratomas, neuroblastomas, hamartomas, and dermoid cysts and similar problems.

When potentially confounding covariables (other than the sampling design variables) were considered, results of analyses were similar to those obtained when they were not considered.

This indicates that the results of this study were not a consequence of confounding by these variables, or factors.

Vietnam veterans who stated that they had contracted malaria while in Vietnam had a higher estimated risk for fathering babies born with hypospadias. No associations were found between the use of malaria chemoprophylactics and the defects risks.

This study provides strong evidence that Vietnam veterans, in general, have not been at increased risk of fathering babies with the aggregate of the types of defects studied here. The use of CDC's birth defects registry precluded the study of other reproductive issues of concern to Vietnam veterans, for example, infertility, or purely functional deficits in Vietnam veterans' offspring.

Assessing Vietnam veterans' risks associated with Agent Orange exposure is difficult. The measures available today for estimating exposure are, at best, imperfect. Thus, we do not know whether the few positive associations found in this study reflect true effects of exposure or merely represent chance occurrences. The fact that Vietnam veterans in general do not appear to have been at increased risk suggests, however, that if effects have been caused by exposure, those effects are small, are limited to select groups of veterans, and/or are limited to rare types of defects.

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