Genetics and counseling in medical practice / Leonard E. Reisman ; Adam P. Matheny, Jr.

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Reisman and Matheny

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January, 1968.

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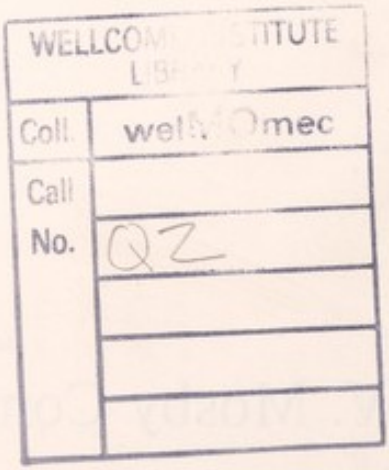

To our wives Alice and Mary

Preface

The purpose of this book is to provide a broad coverage of information that the family physician can use to help people seeking genetic advice. We have tried to orient our discussions of genetic disorders to the topics and questions likely to arise in genetic counseling. To some extent, then, this book is a manual (or perhaps a primer) for genetic counseling in medical practice; it is not an exhaustive treatise on medical genetics.

This book was undertaken with the belief that a discrepancy exists between what is known medically about genetic disorders and the extent to which that knowledge is applied clinically. In our experiences with birth defect and mental retardation programs this belief has been supported time and time again. Countless queries through letters, phone calls, and clinic visits have shown us that in far too many cases of hereditary disorders, genetic advice is not being considered or applied by health professionals.

Our experiences have also taught us that even when some people have been given genetic advice, their subsequent actions indicate that something was amiss in the genetic counseling process. Somehow, genetic advice has not been given or used appropriately. At first we believed that the failures of genetic counseling result from problems of the people counseled: their ignorance, superstitions, emotional reactions, or just plain cussedness. But over the years we have had to amend that initial belief. Too often genetic advice is poorly received or poorly acted upon because it has been poorly communicated.

We recognize that one solution to the problem of making genetic advice available and effective is to increase the number of genetic or heredity clinics. Such clinics have been useful for giving diagnostic as well as counseling services and in providing information to the family physician. Yet, there is a limit to the services these clinics can give. For one reason, they are few in number, and it is unlikely that any crash program will appreciably affect their sparse distribution. For another and more important reason, genetic clinics often provide remote, infrequent, or indifferent contact with the people served. Compared to contact with a physician, people's contact with a genetic clinic can be impractical, impersonal, and impotent.

As many persons recognize, the use of family physicians to impart genetic advice is an attractive alternative to the use of clinics. Physicians are more readily

available in terms of numbers and proximity; their contact or personal rapport with families is more direct; their opportunity for follow-up or extra assistance is more immediate. In many cases, they may be the first to recognize that a genetic disorder exists. Yet the family physician is also limited in that he may have a lack of special knowledge about genetic disorders, or he may feel uncomfortable trying to impart this knowledge and related aspects to the families during genetic counseling.

This book springs from an optimistic view that, despite the wide diversity of topics related to genetic counseling, it is possible to help family physicians and other health team members achieve an overview that will allow them to feel secure about giving advice to families with genetic problems.

The preparation of this book was advanced considerably by the support and encouragement of other faculty members in the Department of Pediatrics of the University of Louisville School of Medicine. Dr. Frank Falkner, former chairman of the department, was especially helpful in reviewing and commenting on specific chapters.

In the same fashion, Captain Joel Vernick, of the National Institutes of Health, provided valuable comments about specific material related to this book.

Among the people who provided technical services for preparation of illustrations are Katherine Baker, John Brown, and Catherine Bauscher, who labored long over tables, photographs, and medical illustrations; Joyce Fullerton and Mary Matheny deserve special praise for providing secretarial help and valuable criticism throughout the tedious preparation of the entire manuscript.

Over the years, other important people and agencies have also helped to support the efforts that culminated in this book. Dr. Madeleine E. Morcy, of the Children's Bureau, and Dr. Jo Anne Sexton and the late Dr. Helen Fraser, both of the Kentucky State Department of Health, have been responsible for creating and maintaining a genetic counseling clinic in Kentucky. Various agencies—Children's Bureau, National Foundation–March of Dimes, WHAS Crusade for Children, Kentucky Heart Association, Kentucky Department of Mental Health, and the University of Louisville School of Medicine—have provided the funds to maintain the counseling program.

Finally, we want to thank all of those parents who have taught us, at each counseling session, something about genetic counseling.

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Contents

Genetics and counseling in medical practice

Chapter 1

Overview

It would be difficult to estimate the number of individuals whose lives will be limited or altered by genetically related disorders. Genetic disorders of "minor" consequence, such as premature baldness or partial color blindness, are quite common and are likely to remain so since they do not interfere greatly with survival in a modern society. The rarer genetic disorders, which are usually the more lethal ones, not only have serious consequences for the afflicted individual but also provoke more serious concern from families and society alike.

Genetic disorders, whatever their frequency or consequences, should not be considered of interest to medical specialties alone. It is not enough to diagnose the disorder, look for a cause, and carry out what ameliorative procedures are available. These disorders affect individuals, their immediate family and relatives, and generations of families. Genetic disorders, therefore, call into play concerns from all aspects of society. The problems of an individual family touch upon broader problems of population genetics, population control, religious prohibitions, economics, social welfare, special education, and medicine. Physicians, nurses, geneticists, psychologists, psychiatrists, statisticians, clergymen, biologists, social workers, educators, economists, and legislators are but a few of the interested parties.

Ultimately, all of our knowledge, our social programs, and our research must reach each of those families affected. It is the individual family that must be helped to understand the genetic problem and act appropriately.

Genetic counseling might be thought of as part of our "helping" activities. Counseling provides the available medical information so that families can understand the nature of the genetic disorder, and it provides guidelines for actions so that families can use the information wisely. In these general terms the process of genetic counseling would appear to be similar to the process of giving any type of medical information and advice. Indeed, this is the case. Genetic counseling appears to be a special preoccupation only because of the relative infrequency of genetic disorders. It is not special because such counseling demands talents outside the capability of the average family physician. To be sure, there are diagnostic problems that may demand extra skills and special knowledge. Once the diagnosis is made, however, the family physician can and many times does conduct genetic counseling.

To say that one need not be a specialist to provide genetic counseling is not to say that the genetic counselor needs no qualifications. The counselor must be informed about genetic disorders, their concomitant conditions, their prognoses, and their likelihood for occurring in present and future family members. In addition, he must be sensitive to the fact that each family with problems constitutes an individual case with its own psychological needs and dynamics. These two qualifications are probably the minimum requirements of the genetic counselor, but they are so important that each one would be of little use without the other. Yet, all too often, one finds counseling situations that emphasize one qualification and not the other. For example, services given at heredity clinics and birth defects centers are invaluable for diagnosing and explaining genetic diseases, but many times the counseling is ineffective because too little is known about the family unit. On the other hand, the family physician, who is aware of, and sensitive to, the family needs, and maintains enduring contact with the family, is often unfamiliar with many aspects of the genetic disorders diagnosed. His counseling is ineffective because it is misinformative.

HISTORICAL PERSPECTIVE

One tends to think of the burgeoning number of genetically oriented clinics as providing evidence for the modernity of the practical application of genetic science. In the history of sciences, genetics is a latecomer; as an applied science, genetics, in the form of clinical genetics and counseling, is certainly a modern medical enterprise. Yet, before there was a science of genetics, man was aware of afflictions that we now know are related to genetic factors. Moreover, genetic counseling, broadly defined, was available in earlier periods of history. Unfortunately, because of the *Zeitgeist* of many of those historical periods, genetic counseling was often an authoritarian and cruel exercise.

Although practices varied from culture to culture and from one period of history to the next, the usual rule was that the birth of a deformed child brought forth disastrous consequences for the child and, usually, the mother. In almost all cases, children with malformations, puny children, and children from multiple births were put to death. This action was justified on the grounds that it was socially or religiously reasonable.

The ancient Babylonians paid particular attention to the births of children with anomalies. From such births they drew presages for any good and evil that would befall the destiny of the king and the country. The diviners compiled extensive lists of abnormal signs that would, if present on the child, have prophetic meaning. Some of these "signs" are commonly found among children with genetic disorders. For example, if a woman were to give birth to an infant that had six toes on both feet, it was taken as a sign that there would be a calamity for the army. Doubtlessly, the removal of such a child was considered essential for an empire whose preoccupation was warfare.

In the *Republic* Plato advocated infanticide for the ill or deformed. Plutarch

relates that the noble Spartan leader, Lycurgus, following the precepts of Aristotle, believed that children belonged to the public instead of to the parents. For the good of the commonwealth, ill-shaped or weak children were taken to a chasm under the mount Taygetus and abandoned. This eugenic measure was taken to assure the health and vigor of future Spartan soliders.

Even during the golden and "enlightened" age of Pericles in Greece, defective and handicapped children were often left to perish on the mountains, or they were thrown into the rivers and seas.

The early Romans considered the birth of a hermaphrodite as an ill omen and usually removed the possibility of misfortune by throwing the child into the Tiber. Other deformed children were similarly in danger when war or a natural catastrophe threatened the empire.

History also indicates that consanguinity has been a topic of interest to people creating rules for marriage. In the ancient Egyptian and the Inca royal families, unions between brothers and sisters were encouraged. Some tribes of fairly recent times have confined marriage to members within the tribe, and thereby they have maintained high consanguineous rates. For example, in one Arabian tribe all members had six digits on each hand and foot. Infants born with a normal number of digits were sacrificed as being the result of an adulterous relation. Another tribe in Southeastern Asia consisted only of members who had tails. Marriage within the family and tribe was so strictly enforced that the birth of a tailless child was evidence for adultery. The tribe killed these children rather than have them held up for public ridicule. For the most part, however, customs and laws regarding consanguinity have generally been prohibitive. At various times drastic measures have been taken to enforce these rules, and guilty persons have been punished by being stoned to death, exiled, branded, or disfigured. It is possible that the foundation of these prohibitions originally came from observations of deleterious conditions in the progeny of consanguineous marriages, but present-day prohibitions seem to be derived from religious principles translated into law. The Roman Catholic Church, for example, prohibits marriage of first cousins except by special permission. This religious rule is also a law in most states in the United States.

The nature of inheritance seems to have been known to earlier peoples. Rules given in the *Talmud* (circa second century A.D.) were given so as to reduce the number of hemophilic children who would bleed to death following the ritual of circumcision. It was stated that circumcision should be omitted for those sons born of a woman who had lost two sons due to bleeding. Sons of the woman's sisters were also to be exempted. The clarity of this rule indicates that the means of inheritance of this disease were fairly well understood. Other historical observers have noted familial inheritance of facial characteristics, stature, diseases, and a host of other human traits. One of the earliest historians, Pliny the Elder, was aware that the occurrence and placement of some moles and birthmarks could be transmitted through several generations. Unfortunately, some of these historical

Fig. 1-1. A, "Bird-boy." **B,** "Dog-boy." (From a drawing after Paré; courtesy W. B. Saunders Co., Philadelphia, Pa.)

observations were erroneous and led to the social ostracism of some persons who were thought to carry the familial "taint" of a disease. For example, some parents exercised extreme caution in revealing that a relative had a disease such as cancer, so that their children would not be considered undesirable marriage candidates because of it. Similar biases are not uncommon even today.

Finally, we should not overlook the cases of congenital malformations described in the past that gave rise to dire superstitions and beliefs still encountered today. Ancient beliefs regarding the human's association with animals or demons helped to "explain" the presence of such malformations as phocomelia, hairy nevi, clubfeet, and polydactylism. The numerous legends concerning satanic monsters doubtlessly sprang from overenthusiastic descriptions of these malformations. One wonders whether the "bird-boy," as depicted by Paré (Fig. 1-1, *A*), was a fabulated account of a case of congenital ichthyosis. Also, the "dog-boy," as depicted by Paré (Fig. 1-1, *B*), bears some descriptive resemblance to a child with the Cornelia de Lange syndrome, which, incidentally, may be the modern disease for those cases represented in legends about "werewolves." Circus "freak" shows still provide us with examples of the ignorant and superstitious exploitation of human abnormalities.

THE NEED FOR GENETIC COUNSELING

From our view of history, most of the humans with genetic "mistakes" were not likely to lead normal lives. Many were likely to die in early life from natural causes. Others were likely to be killed, exiled, or ostracized because of the

"counseling" considerations mentioned: population control, improvement of the breed, religious prohibitions, or attempts to placate satanic or demonic forces. By whatever natural or social means, the hapless individual was removed from his family or community. The parents had little choice.

In modern times, the startling armamentarium of medical science is used to keep alive many children who would have died from genetic diseases. Medical science thereby offsets nature's selective way of tidying many of its genetic mistakes. Moreover, modern ethical practices, those of the Nazi era notwithstanding, prohibit the drastic eugenic measures taken throughout history to remove genetic mistakes. Consequently, more children with deleterious genetic endowments are likely to be maintained to the point that they may have offspring of their own. Not too long ago, half of all the victims of fibrocystic disease died in infancy. Therapeutic advances in the treatment of this disease are now reaching the point that increasing numbers of patients will reach the age for reproduction. Their offspring will add to the load of this recessive disease in the population so that, in the future, this disease is likely to be more common than the present rate of one diseased child per 1,000 to 2,000 live births. Therapeutic advances in the treatment of pyloric stenosis and diabetes are producing a similar effect.

Until we discover some means to correct defects in the genetic constitution of affected families, the present medical achievements make it quite clear that there is going to be an increase in the numbers of families needing genetic advice. This increase is over and above the growth in the need for counseling imposed by those patients who have genetic diseases with a constant base rate of occurrence. The latter afflicted persons may represent a fixed *percentage* of the population, but their total *numbers* will rise as the size of the population increases, a trend that shows no sign of being reversed.

Comprehensive public health programs will add to the counseling load too. These programs have become more aggressive about case finding, and each day, even in those areas with adequate medical services, "hidden" patients with genetic disorders are being brought to light. Likewise, health programs taken to isolated communities that had little or no medical scrutiny before will uncover new cases of old genetic disorders and perhaps find new disorders. Without doubt, these programs will find factors of heredity to be linked to human afflictions, medical and social, not now believed to be genetically determined.

The community mental retardation centers, birth defects centers, and other "mission-oriented" units also add cases to the genetic counseling load every day. The local physician, both in his practice and in his referrals, entertains genetic hypotheses for some of his patients' diseases. The family doctor and the specialist in clinical genetics are also being presented with more and more questions about genetic factors pertaining to medicolegal problems, adoption, old age, population control, determination of family size, and mutagenic hazards, all of which will invariably lead to further demands for genetic counseling.

Finally, we should not forget that the average citizen is becoming better in-

formed about medical matters. Every communication medium presents medical information in factual or fictional form. Sometimes this public information is so current that people are aware of some new medical findings before their physicians get around to the same material in the technical journals. The "informed" citizen will want to know more about the problems he has or might have in his family. Urbane parents are not likely to settle for a diagnosis of their children's afflictions; they want to know the causes, the treatments, the prognoses, and the chances of recurrence. When these afflictions are related to genetic factors, the person attempting to answer the parent's question has become a genetic counselor, whether or not he is trained as a geneticist or as a counselor.

As a consequence of all these factors, the future influx of patients will swamp existing programs unless we anticipate future needs. This anticipation need not dwell on the increase in the number of special genetically oriented "centers" alone. More centers will undoubtedly be needed, but there are practical limitations on the number of centers we can afford and the number of centers we can staff, given our present production of medical personnel. Our future needs can be met if we bring the family physician or "general practitioner" back as an active member of the "genetic team." We considered above that the family physician has a vital role because he is likely to know most about the family needs and is in a position to maintain enduring contact with the family. Now we can add that family physicians constitute an available source of manpower to meet our future needs.

Another source of personnel to meet the future needs of medical genetics can be found among other members of the health professions. Nurses, medical technicians, guidance counselors, and social workers are in a unique position to be trained to become capable members of a "genetic team." The short supply of physicians makes us think that these "helpers" should be so trained. They, with supervision, can perform much of the labor involved in clinical genetics. One can entertain the thought that some health personnel, such as nurses or social workers, might even become genetic counselors. After all, counseling techniques are part of their stock in trade.

A constructive appraisal of the future needs of medical genetics indicates that we have choices of three programs: we can obtain more geneticists who are trained in counseling techniques, we can obtain more physicians who are trained in genetics and counseling, or we can obtain counselors who are trained in genetics. The present and anticipated demands for genetic counseling lead us to believe that we should choose all three.

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Chapter 2

Clinical tools for genetic counseling

It has been said that technology often paces science. Medical or clinical genetics, as one of the applied sciences, has progressed only as far as the applications of techniques (and inventions) have permitted. Some of these applications or clinical "tools," such as making a pedigree or taking a medical history, are quite simple. Others, such as chromosome analysis, are conceptually simple but demand skilled procedures and special equipment. In this chapter, we will describe some of the more common clinical techniques employed to diagnose genetic disorders.

An understanding of the techniques available to clinical genetics is essential to effective genetic counseling. Such an understanding will promote the counselor's confidence in the diagnostic information that he is to relate to the families. It is not likely that a physician can sound convincing about a diagnosis if he is unaware of, or vague about, the steps leading to the diagnosis. The counselor's own lack of conviction can be conveyed to the family in obvious, and sometimes subtle, ways. The physician who quickly bypasses what the diagnostic procedures were, airily dismisses the procedures involved as being too complicated to explain, or frankly confesses that he does not know what the procedures entailed conveys to the families a sense of uncertainity. They, in turn, may become uncertain about all aspects of the counseling and look elsewhere for information. Like many of us concerned with other kinds of problems, families with genetic disorders want advice from people who "know what they are talking about."

It has been our experience that explanations and demonstrations of the diagnostic techniques can augment counseling. The diagnosis of D-trisomy syndrome can be made much more meaningful to parents when they are shown a karyotype of the chromosomes. Many families are intelligent enough to understand the differences indicated between normal and abnormal dermatoglyphics. Intelligent or not, almost all families are curious about why blood, buccal smears, palm prints, footprints, photographs, and family pedigrees are taken. It does no harm to relieve their curiosity, and, indeed, most seem to profit from this informative experience.

The differential diagnosis of genetic disorders depends on two main sources of information: familial data derived from a history of the family's, and possibly

the relatives', medical events, and "laboratory" data derived from clinical procedures. This chapter, which describes techniques applicable to both of these sources of information, is written for the family physician. It is not expected that the description of the techniques will enable the physician to put all of them into practice. Some techniques, such as taking photographs, creating a pedigree chart and analyzing dermatoglyphics, the physician can, or may presently, use. All physicians certainly obtain a family history. A chromosome analysis is likely to be out of the question for most physicians. In any event, the descriptions offered here can enable the family physician to understand the relative importance of the different sources of clinical information.

MEDICAL HISTORY AND PEDIGREE

Despite our application of the term "technique" to the process of taking a medical history or of obtaining a medical pedigree for genetic purposes, neither procedure involves highly specialized technology. The term "technique" is appropriate, however, because the medical information needed for genetic counseling must be acquired in a more studied fashion than the information gleaned by the usual history-taking approaches. First of all, the physician, nurse, or another trained person must allow a liberal amount of time in getting this information. Secondly, it is best to get the information carefully and systematically from *both* parents. Medical records and family bibles may be referred to, and other relatives may be consulted for additional information. These sources may be especially helpful when consanguineous marriages are indicated or when multiple marriages with several sets of offspring have occurred. These relationships should be outlined with extra care. Information about members of the immediate family or relatives who have died at early ages should be noted in detail. Medical records or a coroner's report can be helpful in these cases.

The content of the medical information to be obtained can be considered as belonging to two classes. The first class is the family pedigree, which traces associations among the family, relatives, and ancestors. The second class is the medical history of the mother's previous pregnancies, her pregnancy that resulted in the afflicted person, and those pregnancies of relatives that resulted in disorders.

Family pedigree

The family pedigree or "family tree" can be obtained and summarized in an outline or chart that contains symbols showing the family members, the relations between family members, and available vital statistics on the family members. Sex is indicated by the symbols used. Age or the dates of birth and death are often noted for each family member. Symbols commonly used to make such an outline are shown in Fig. 2-1. Some types of pedigrees may include special symbols or variations of the symbols found in the figure, but these special usages are usually explained in the material.

The use of the pedigree symbols is shown by Fig. 2-2, which depicts an

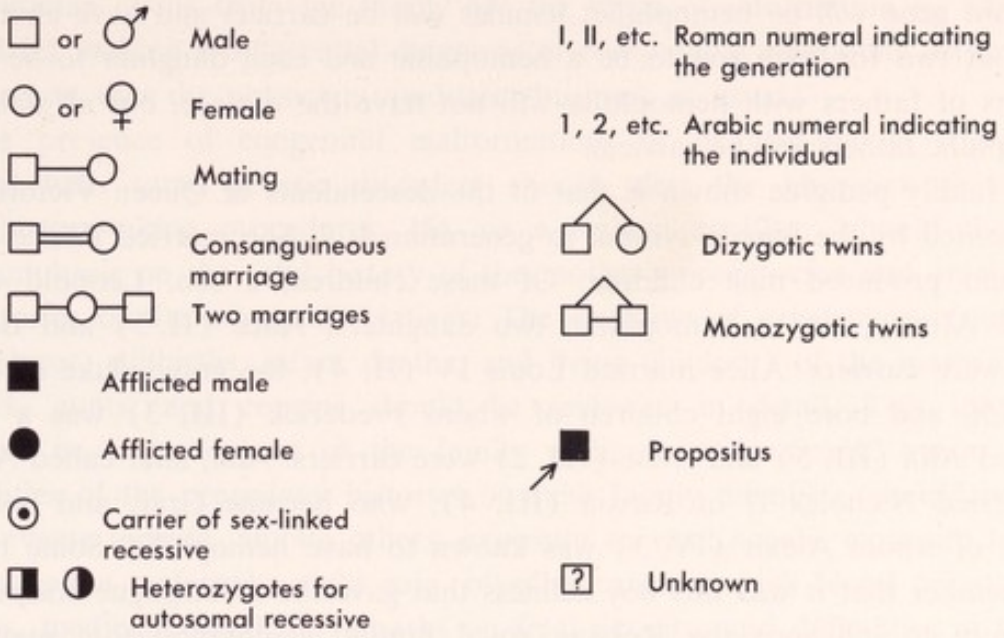

Fig. 2-1. Symbols and conventions commonly used in making family pedigrees.

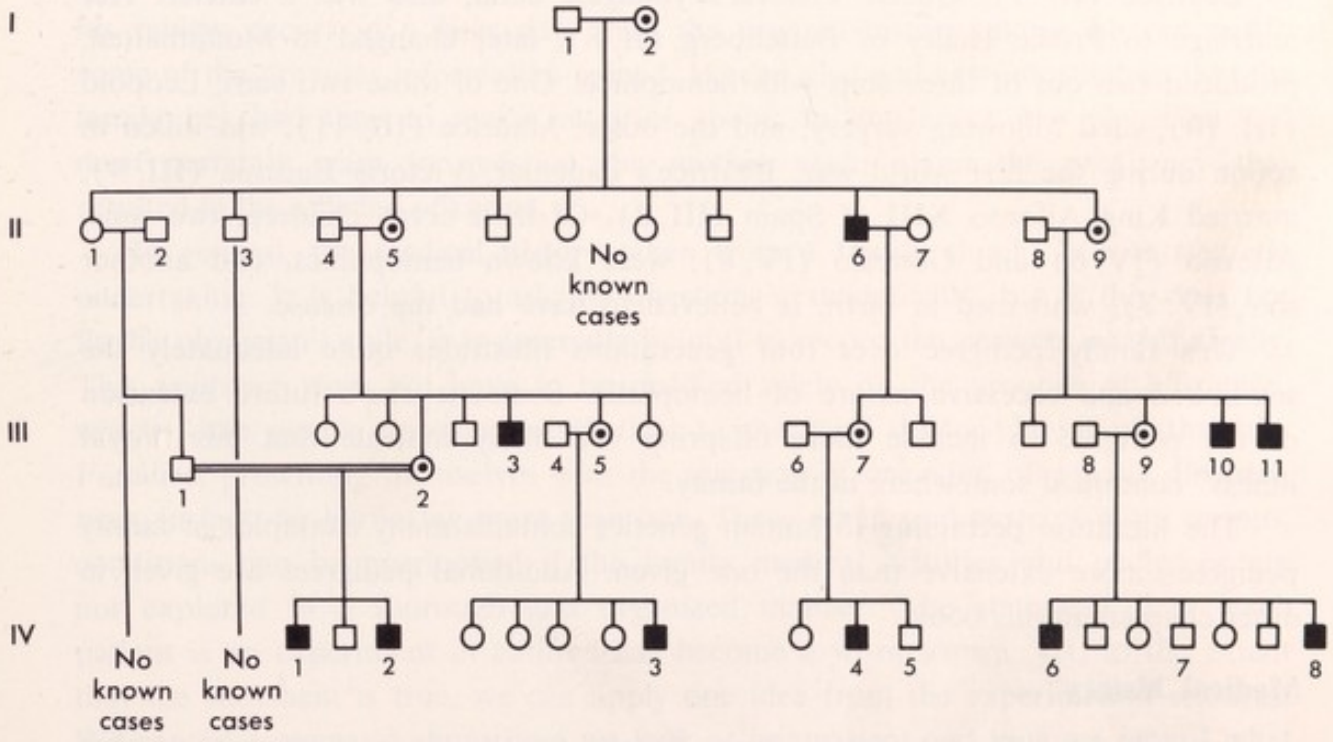

Fig. 2-2. Pedigree of hemophilia among the royal families of Europe.

illustrious family history that had many instances of hemophilia. Hemophilia is a sex-linked, recessive defect resulting from a mutation in the X chromosome contributed from the egg of the mother or the sperm of the father. Males carrying the mutant gene will be hemophilic; females will be carriers and have chances of one out of two for each son to be a hemophilic and each daughter to be a carrier. Sons of fathers with hemophilia will not have the disease, but all daughters of hemophilic fathers will be carriers.

The family pedigree shown is that of the descendents of Queen Victoria who is represented by the female symbol in generation I, 2. She married Prince Albert (I, 1) and produced nine children. Of these children, a son, Leopold (II, 6) Duke of Albany, was a hemophilic; two daughters, Alice (II, 5) and Beatrice (II, 9) were carriers. Alice married Louis IV (II, 4), the grand duke of Hesse-Darmstadt, and bore eight children of whom Frederick (III, 3) was a hemophilic and Alix (III, 5) and Irene (III, 2) were carriers. Alix, later called Alexandra, married Nicholas II of Russia (III, 4), who became Czar, and bore five children, of whom Alexis (IV, 3) was known to have hemophilia. Some readers will remember that it was this boy's illness that gave the mystagogue Rasputin an opportunity to influence the Russian royal family, a situation that may have hastened the Russian Revolution. Irene married a cousin, Prince Henry of Prussia (IV, 1), and bore two hemophilic sons, Waldemar (IV, 1) and Henry (IV, 2).

Leopold, the hemophilic son of Queen Victoria, married Princess Helen of Waldick-Prymont (II, 7). The union produced a daughter, Princess Alice of Teck (III, 7), who was a carrier. Her marriage to the Earl of Athlone (III, 6) resulted in one known hemophilic son, Rupert, Viscount Trematon (IV, 4).

Beatrice (II, 9), Queen Victoria's youngest child, also was a carrier. Her marriage to Prince Henry of Battenberg (II, 8), later changed to Mountbatten, produced two out of three sons with hemophilia. One of those two sons, Leopold (III, 10), died following surgery, and the other, Maurice (III, 11), was killed in action during the first world war. Beatrice's daughter, Victoria Eugenia (III, 9), married King Alfonso XIII of Spain (III, 8). Of their seven children, two sons, Alfonso (IV, 6) and Gonzalo (IV, 8), were known hemophilics, and another son (IV, 7), who died at birth, is believed to have had the disease.

This family pedigree over four generations illustrates quite adequately the sex-linked and recessive nature of hemophilia. Someone else's future extension of the pedigree to include more offspring will likely indicate that this "royal illness" continued somewhere in the family.

The literature pertaining to human genetics contains many examples of family pedigrees more extensive than the one given. Additional pedigrees are given in other chapters in this book.

Medical history

It would be difficult to establish any criteria for the kinds of information that the physician should obtain for a medical history related to genetic disorders. In

usual practice, a medical history is often obtained prior to, and for the purpose of, making a diagnosis; i.e., the medical history helps to establish that the disorder is genetically determined in the first place. Therefore, the kinds of information that the physician elicits from the family are the kinds of information he has always elicited for making a differential diagnosis of comparable conditions. In this sense, one can say that the physician conducts "business as usual."

The presence of congenital malformations or of well-known stigmata associated with some genetic disorders should alert the physician to alter his usual history-taking procedures. He, or a trained ancillary, should then place more emphasis on the total history of the mother's pregnancies and on the medical histories of the maternal relatives. The outcome of pregnancies (number of miscarriages, stillbirths, infant deaths, and living children) of the mother, grandmothers, aunts, and cousins should be reviewed in detail. This information will also be kept as part of the family pedigree. "Significant" events, or abnormalities of the pregnancy histories of these family members, should be noted. These events include, among others, exposure to viral agents, exposure to radiation, excessive maternal weight gain, bleeding, anemia, high blood pressure, convulsions, medications taken, remarks on fetal activity, and difficulties at the time of delivery. Diseases, causes of death, and ages at death of family members on the paternal and maternal sides of the family should be obtained for the history and the pedigree. The importance of obtaining a history of the father's exposure to ionizing radiation should not be overlooked.

Needless to say, these kinds of information to be elicited from the families are a minimum. Yet, it will require some time for anyone to obtain the information. Afterwards the physician can quickly review the history with the family. If his review occurs at a later date than the original history-taking, he can verify some of the previous information gained. He can also add new information that the family has had time to make inquiries about. In any event, the physician will most certainly want to question the mother again about the pregnancy that resulted in the afflicted offspring.

In general, the medical history taken from a family should be a systematic undertaking. It is helpful to ask the questions systematically, but if this does not fit the physician's style, it is assuredly helpful to record the answers systematically. This approach does not have to be justified solely on the grounds of efficiency, which some people consider antithetical to the ideal doctor-patient relationship. Families, presenting themselves with the question of one kind of genetic disorder, may, in fact, be harboring more than one. These other, and perhaps more serious, conditions can be overlooked if the family medical histories and pedigrees are not explored in a thorough and organized manner. The statement that "each patient is an experiment in nature" has become a worn truism; yet, to the extent that the statement is true, we can apply one idea from the experimental sciences. We can be systematic about how we look at our patient and how we record what we see.

Photographs

Photography is an obvious and quite useful tool for physicians to employ for the analysis and description of medical information pertaining to genetic disorders. Photographs of the patient as well as of immediate family members do much to highlight verbal descriptions of some diagnostic findings. This is particularly true when qualitative verbal descriptions are used. The verbal descriptions of such features as "low-set" ears or "wide-set" eyes are usually vague, but photographs help to clarify the descriptions. Physical descriptions of abnormalities, such as clinodactyly, syndactyly, polydactyly, micrognathia, epicanthal folds, hypertelorism, mongoloid or antimongoloid slant of the eyes, webbing of the neck, and others, can be augmented quite graphically by photographic means. This point can be emphasized by the clinical information available in the photograph of the child in Fig. 2-3. In some cases, the unusual facies of a patient or the "funny-looking kid" may appear more obvious by looking at a photograph than by looking at the person. Asymmetry of body parts and unusual postures likewise seem to "stand out" more in some photographs.

Photographs, in addition to being useful as descriptive and diagnostic aids, also serve to provide longitudinal information about children with birth defects or with stigmata associated with syndromes having a known outcome. Photographs included in the medical record of these persons can prove to be of as much value in many cases as much of the recorded medical history.

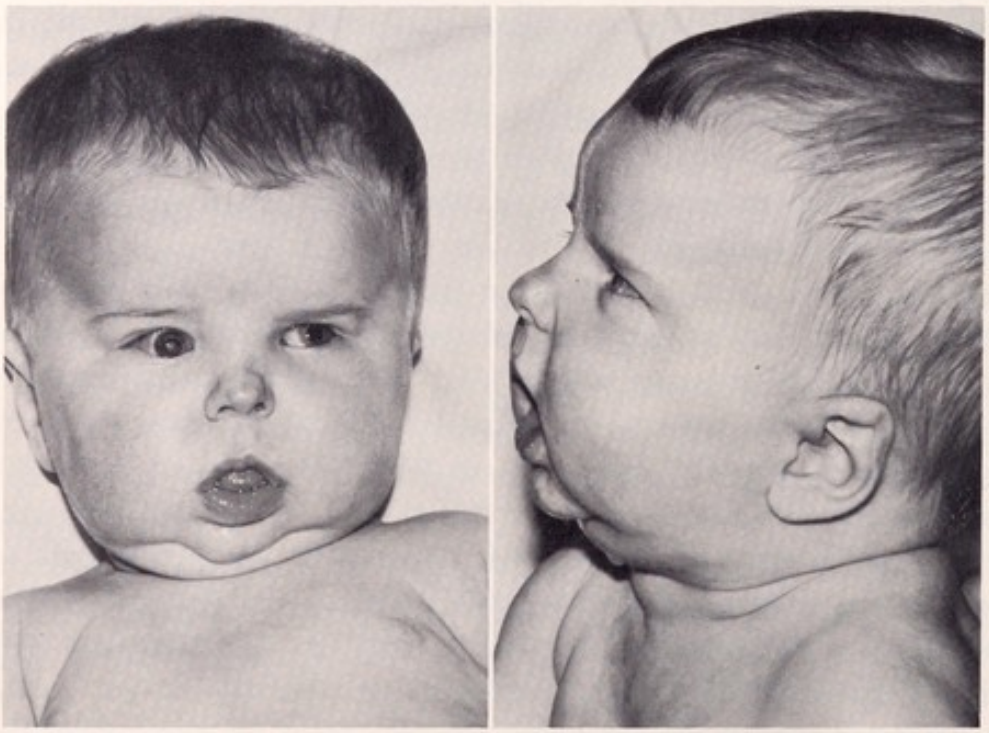

Fig. 2-3. The Hallerman-Streif syndrome (oculomandibulodyscephaly). Note the "birdlike" facies, scanty hair, cataract in the right eye, and strabismus, which characterize this syndrome.

It is surprising that more physicians in private practice or even physicians in medical institutions do not routinely include photographs of patients. The use of an inexpensive Polaroid camera would enable a nurse or secretary to achieve rather good photographs in short order. As we mentioned earlier, when heredity seems involved, photographs of other family members can be made in the same simple manner.

Dermatoglyphics

One of the simpler techniques that the family physician can use involves the collection of handprints and footprints for dermatoglyphic analysis that can be made at a genetic clinic. Dermatoglyphics (Greek for "carving on the skin") originally referred to the study and classification of patterns on the fingers, palms, toes, and soles made by dermal ridges. General practice now includes flexion creases within the scope of dermatoglyphics. The study of dermal patterns may appear very much like palmistry, but unlike that antique exercise, the scientific merit of dermatoglyphics is well established. Cummins, who coined the term dermatoglyphics, was the first to show that patients with Down's syndrome have definite sets of dermal patterns that differ from the dermal patterns of normal persons. More precise mathematical analyses of dermal patterns of mongoloids indicate that one can pick out about 70% of the people having this disease on the basis of the dermal patterns alone. Obviously, this is a success ratio that any palmist would secretly envy.

The classification of dermal patterns has been found to be useful for the detection and study of chromosome disorders other than Down's syndrome. Also,

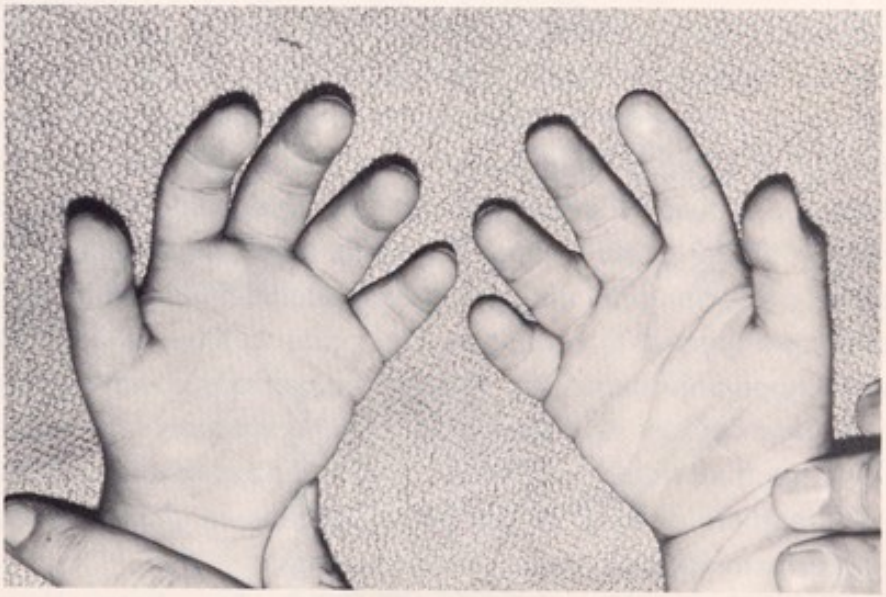

Fig. 2-4. The single transverse palmar creases (simian lines) found on both palms of a child with Down's syndrome. Note also the short, stubby fingers and the incurved fifth finger (clinodactyly).

abnormalities in the dermal patterns are described for a number of disorders that do not necessarily manifest visible chromosome defects. Some of these disorders are pseudohypoparathyroidism, Wilson's disease, Cornelia de Lange's syndrome, and various conditions in which congenital heart disease is found. We should also note that disorders not related to genetics but due to toxic or viral agents can find expression in dermatoglyphic stigmata. Mothers exposed to rubella or mothers ingesting thalidomide during pregnancy have been found to have offspring with abnormal dermal patterns.

The fact that there are several diseases for which one can find abnormal dermatoglyphics does not mean that there is necessarily a characteristic dermal pattern for a specific disease. Moreover, an individual's abnormal dermal pattern does not necessarily indicate that he manifests a disease of *any* type. It should be appreciated that "abnormal" dermal patterns can occur in normal persons. Dermal patterns are called "abnormal" when they are relatively rare in the normal population; individuals are not necessarily called abnormal because they have such patterns. For example, it is a common finding that about one-half of the patients with Down's syndrome have a single transverse palmar crease (Fig. 2-4) instead of the two normal creases. This finding, however, does not mean that normal-appearing people with such a crease have latent Down's syndrome. About 1% of normal Caucasians have such a crease, and it is suggested that a slightly greater percent of Orientals may display the same sign. In the absence of other clinical symptoms in the patient or in the family, the interpretation of dermatoglyphics should give due consideration to parental and racial patterns. Unusual dermal patterns, then, should be considered as suggestive signs of a disorder; they do not provide for diagnostic certainty.

The development of dermal patterns is related to the differential growth of a number of structures, occurring between the third and seventh months of fetal life. Abnormalities in the general growth process, which includes skeletal and muscular growth, apparently lead to abnormalities in the differentiation of the dermal ridges. These dermal abnormalities are thought to be consequences of developmental disturbances occurring prior to or during the time period mentioned. It would follow that unusual dermal patterns are significant indicants of developmental anomalies taking place during fetal life. For this reason, children with major congenital malformations not specifically related to chromosome or genetic disorders would be expected to have, and are found to have, a significant number of unusual dermatoglyphic markings. During this period, however, growth variations due to a combination of parental or racial genotypes can lead to a copy of a dermal pattern that would be classified as a dermatoglyphic abnormality. As we pointed out earlier, unusual or minor alterations in dermal patterns, while rare, are not necessarily indicative of a disease process.

The presence of specific dermal anomalies has been shown to be less significant than the frequency with which certain patterns appear on the fingers, palms, etc., and the combination of various dermal patterns found. For

example, the presence of a fingerprint arch is not an unusual pattern per se; but an increased number of arches (more than six) has been noted to be rare in the normal population, while common to patients with D-trisomy, Cri du chat, and Klinefelter's syndromes. These three syndromes also show abnormal, but dissimilar, axial triradius patterns. Therefore, by combining the presence and frequency of arches on the fingers with the presence and type of an abnormal axial triradius pattern, one could isolate one or a few of many disease conditions.

The following sections will present a simple description of the important dermal patterns of interest to the clinical geneticist and the genetic counselor. A more detailed discussion of the patterns and their interpretation can be found in the selected readings suggested at the end of this chapter.

Fingerprints. Fingerprints can be classified by the presence of whorls, loops, and arches. Loops can be further differentiated by the side that is open relative to the radial or ulnar side of the finger. Fig. 2-5 illustrates the whorls, loops, and arches of the finger. The size of the dermal pattern is also important; this is expressed by a ridge count. The ridge count is obtained by counting the dermal ridges intersecting a line drawn on the fingerprint pattern from the triradius to the center of the core pattern of the whorl or loop. Such a count can be made only for whorls or loops, since the arch has no triradius. In counting dermal ridges, the dermal ridge forming the triradius and the core pattern are not counted. Fig. 2-6 illustates how a ridge count is made.

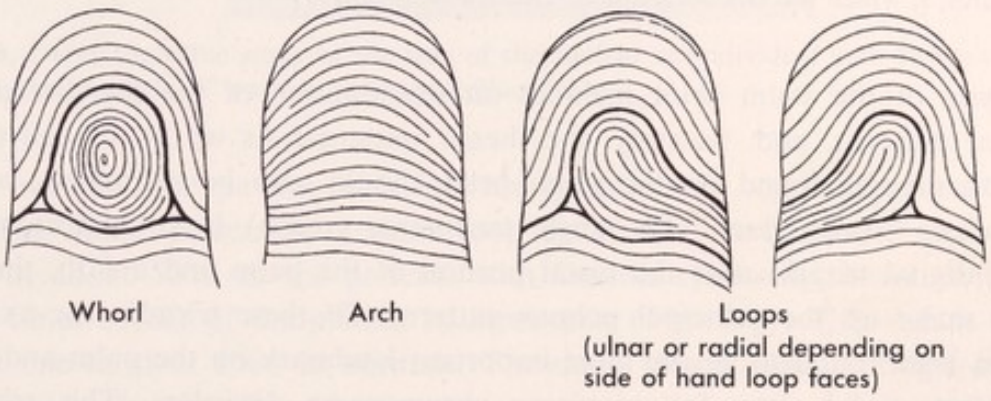

Fig. 2-5. The basic types of digital patterns that are of great diagnostic importance in the various chromosomal abnormalities.

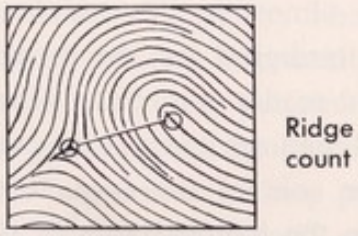

Fig. 2-6. Digital ridge count. The digital ridges are counted by drawing a straight line between the center of the pattern and the triradius.

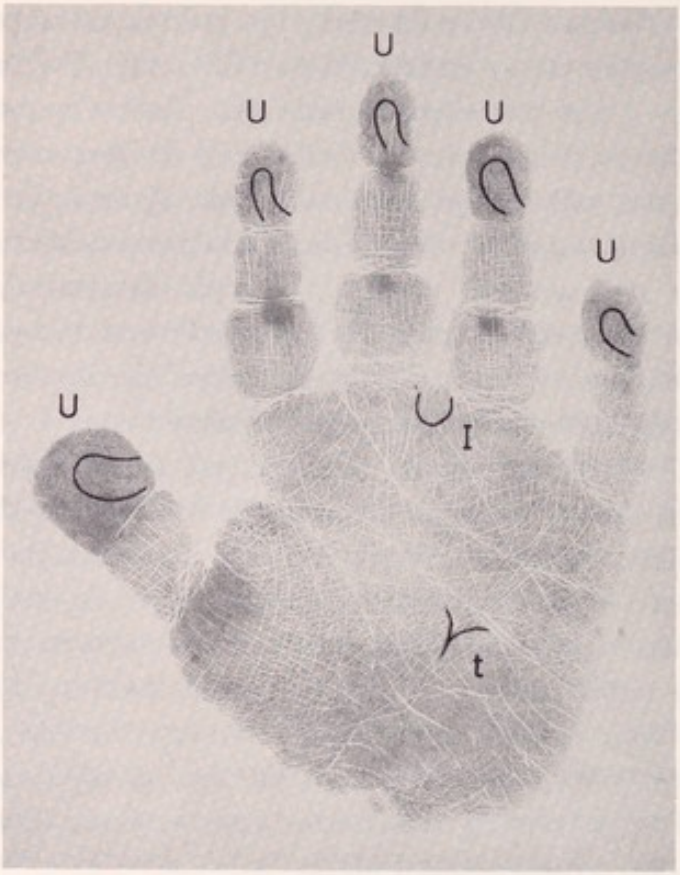

Fig. 2-7. Palm print demonstrating the ulnar loops, **U,** third interdigital loop, **I,** and distal axial triradius, **t,** which are characteristic of Down's syndrome.

Analysis of the palm print includes an examination of the five triradii, the interdigital patterns, and, possibly, the thenar patterns. As we mentioned earlier, the flexion creases found on the palm print should also be examined, because the so-called "simian line" (the single transverse crease) is an important sign. The four digital triradii near the distal portion of the palm and a fifth, the axial triradius, make up the principal palmar patterns. Of these triradii, the axial triradius has been found to be the most important landmark on the palm and is one of the most useful signs for screening chromosome disorders. This triradius, normally found close to the base of the palm proximally near the wrist crease, has a more distal location on the palms of patients with trisomy 21, 18-trisomy, Cri du chat, D-trisomy, and other syndromes. For example, the triradius in trisomy 21 (Down's syndrome) lies almost in the middle of the palm (Fig. 2-7). The other palmar patterns, the interdigital and the thenar, are of less consequence for this discussion. The interested reader can refer to them in the appropriate chapters in this book or in the selected readings given at the end of this chapter.

Footprints. Prints of the sole of the foot are of some interest because of abnormal variations found in the hallucal area of the sole. Patterns in the calcar area are extremely rare. In the hallucal area the most common patterns are distal loops with a high ridge count (indicating that the patterns are large) and tibial or

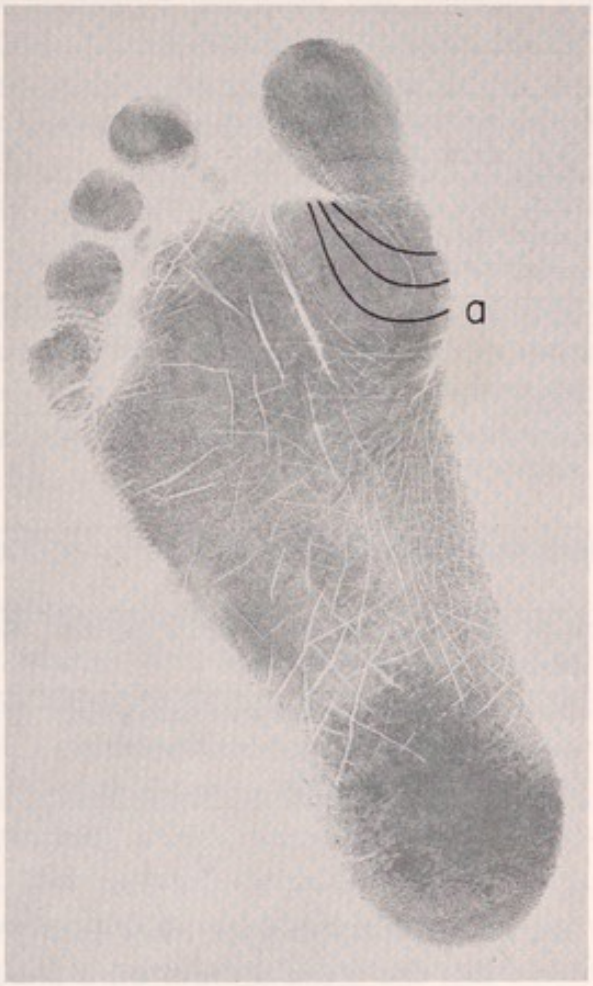

Fig. 2-8. Dermatoglyphic study of the sole of the foot of an individual with Down's syndrome showing the "arch tibial" pattern, **a,** in the hallucal area.

fibular whorls. The patient with Down's syndrome is commonly found to have the "arch tibial" pattern or a small loop distal. The "arch tibial" sign, which is found in about 50% of the patients with Down's syndrome, is an arch opening to the tibial border of the plantar hallucal area (Fig. 2-8). This sign is very rare (about one third of 1%) in normals. The small (fewer than 20 ridges by count) loop distal is often a hallucal pattern for mongoloids.

Other unusual findings from plantar prints of patients with various syndromes can be found in Table 2-1. Needless to say, the table is suggestive and not exhaustive. Also, examination of the table would lead one to believe that a specific plantar pattern is related to a specific disorder. The evidence to date seems to support this point; yet the lack of detailed information about controls ("normal" people) and the evidence that some of these patterns occur in patients with other disorders must make one wary about using the patterns for diagnostic specificity.

Techniques of printing. The practice of making prints for the medical records of patients referred for genetic disorders is a good one, just as is the practice of keeping other kinds of clinical data. Despite the difficulties of obtaining clear prints from babies and the awkward aspects of obtaining prints of the feet, making

Table 2-1. Chromosome disorders and associated dermatoglyphic patterns

	Hands	*Hallucal area of sole*
D_1 trisomy	Simian line; increased number of arches on digits; distal axial triradius	Loop tibial or arch fibular pattern
18-trisomy	Simple arch pattern on digits (generally greater than 6); single flexion crease fifth finger; simian line	Open field
Down's syndrome	Excess ulnar loops; simian line; distal axial triradius; single flexion crease on fifth finger; third interdigital loop	Arch tibial or small loop distal
Cri du chat (deletion short arm of No. 5)	Simian line; distal axial triradius; increased number of arches on fingers	Open field
Deletion long arm of No. 18	Excess whorls; simian line	Open field
Klinefelter's syndrome	Loops with low ridge counts and increased number of arches on digits	No characteristic finding
Turner's syndrome	Distal axial triradius; increased number of whorls on digits; full or partial simian line frequently present	Loop distal or whorl

and collecting prints can be advantageous for more than research purposes. For example, unusual patterns that the clinician finds on a patient may be related to familial or racial characteristics. Unless he lines up all the relatives at the same time and looks at their patterns, the clinician runs the risk of forgetting some of the pattern characteristics from one person to the next as he sees them on different occasions. Moreover, "microsymptoms," or dermatoglyphic abnormalities, of Down's syndrome and other conditions may appear in normal relatives to some degree. The "microsymptoms" afford clues to the hereditary basis of some of the disorders, and, therefore, should not be overlooked. Unless one keeps an extensive description record of each visual examination of the dermal patterns of relatives, the absence of prints may cause the clinician to overlook these minimal signs. Certainly, the calculation of ridge counts, the exact placement of the axial triradius, and other detailed analyses would be very difficult by inspection alone.

The most common method for obtaining prints is the one used by police around the world. One needs only fingerprint ink, a roller, a glass plate, paper, and a sponge. The ink is rolled out onto the glass, and the palm, finger, or foot is placed lightly on the ink. The paper is placed over the sponge so that when the hand or foot is placed on the paper, the sponge will depress, and concave areas of the foot and hand will register. Fingers are usually rolled across the ink and consequently rolled across the paper. All prints should be inspected so that smudged or incomplete prints can be redone.

An inkless method, the Faurot method, makes use of a special fluid and

sensitized paper. This method is less messy but demands more cooperation from the person to be printed. Young children and babies are difficult to print by this method. Its use entails rubbing the palm or sole with a cloth pad soaked in the fluid and then lightly pressing the area on the sensitized paper.

Young infants, newborns, and stillborns present the most difficulties for making prints. A method that employs a porous ink pad and high-quality, glossy paper has been found effective when the infant's skin surface is prepared for printing. The skin surface should be warm, clean, and dry for making good prints. This method, which takes some time and effort, has been superseded by an inkless photographic technique that utilizes optical means for enhancing the contrast of dermal patterns. These patterns are photographed on Polaroid film, which yields a good print rather quickly.

NUCLEAR SEX DETERMINATION (SEX CHROMATIN TEST)

A sex difference in mammalian cells was first recognized, almost accidentally, in 1949 by anatomist Murray Barr and his graduate student, E. W. Bertram, who were conducting some experiments on nerve fatigue in domestic cats. The sex difference consisted of a small body in the interphase nuclei of the cat nerve cells, which invariably disappeared during mitosis. This "sex chromatin body" or Barr body, as it is very generally called, was soon found to distinguish between the males and females of other species, including dog, skunk, gorilla, and, of course, man. Although the nature of this sex chromatin body was not clearly understood for quite a few years, it is now believed that the mass is derived from a single X chromosome. In the normal female, one of the pair of X chromosomes in each cell coils up tightly, for a time, into a small (and genetically inert) mass of chromatin material. The mass is absent from nuclei of normal males.

In addition to its utilization as a "marker" in sex identification, examination of

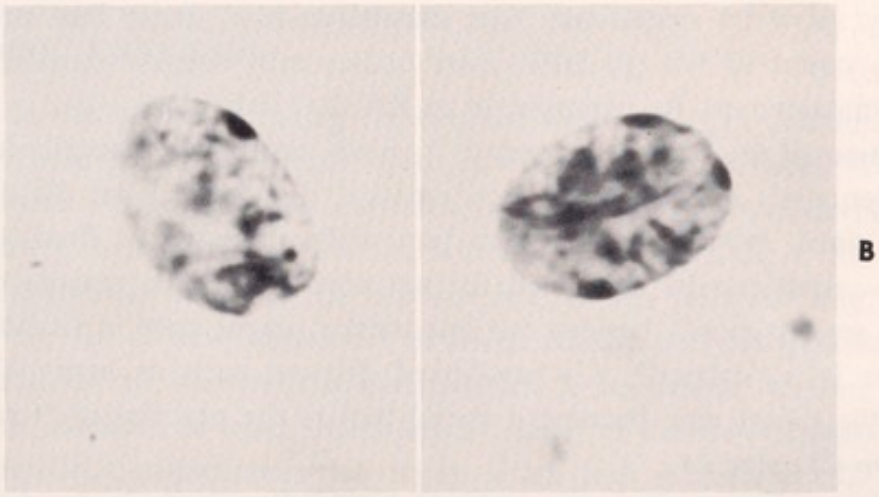

Fig. 2-9. A, Interphase nucleus of a buccal mucosal cell from a normal female. The mass of sex chromatin lies against the nuclear membrane. **B,** Buccal cell from a female with XXXX chromosomes. This contains three sex chromatin masses.

cell nuclei for chromatin bodies provides a relatively rapid and inexpensive aid in the diagnosis of sex chromosome abnormalities. The number of Barr bodies is directly related to the number of X chromosomes in the individual's chromosomal makeup, the relationship being N-1 (where N is the number of X chromosomes). Thus, if the person has three X chromosomes, as in the triple X female or the XXXY male, two Barr bodies will be seen in the cell nucleus; in a quadruple X individual, three Barr bodies will be seen, and so on (Fig. 2-9). In individuals with an XO sex chromosome complement (Turner's syndrome), just as in the normal male (XY), the sole X chromosome presumably remains genetically active (and dispersed throughout the nucleus) during interphase. It never forms a sex chromatin mass. The analysis of sex chromatin in cells can give a helpful clue for the diagnosis of sex anomalies, since one can accurately predict the number of X chromosomes and detect abnormalities of the X chromosome simply by looking at a cell smear.

The Barr body can be demonstrated in almost any tissue, but the buccal smear technique provides a conveniently simple method. The mucosal cells, scraped from the inside of the cheek, can be spread on a slide, "fixed" in alcohol, stained with a variety of basic dyes (with an affinity for DNA), and be ready for study within several hours. The references at the end of this chapter should provide at least several satisfactory procedures for the reader who would like to do the Barr body test himself. The sex chomatin itself can be seen under the oil immersion objectives of an ordinary light microscope. It lies flattened against the nuclear membrane. It is also somewhat triangular in shape and is about 1μ in size. An unusually enlarged sex chromatin mass may be a good clue to an uncommon morphologic abnormality of the X chromosome. One such enlarged Barr body, an isochromosome X, which has two pairs of long arms instead of a long arm and a short arm, is associated with Turner's syndrome. "Normal" Barr body counts may vary from laboratory to laboratory. In our own laboratory, female counts range from 25% to 75%, with an average of approximately 40%. Normal males may show an occasional "sex chromatin–like" mass that probably is an artifact. A count of 5% to 20% Barr bodies may suggest mosaicism involving the X chromosome, as, for example, in an XX/XO individual.

Prediction of the baby's sex before its birth, until now generally left to "signs" like the frequency of the baby's movements ("if it kicks a lot it's a boy"!), can be made much more accurate. The fetal cells in amniotic fluid samples from pregnant women can be examined for sex chromatin. The reasons for obtaining a prenatal sex diagnosis, besides our impatience, might arise in situations in which the mother is a "carrier" of a sex-linked disease, such as hemophilia. Prenatal sexing of the infant may become a useful tool in the practice of "fetal medicine," discussed in Chapter 14.

An analogous sex difference as shown by the Barr body is present in the polymorphonuclear leukocytes. A small percentage of female white blood cells show a little appendage or "drumstick" (Fig. 2-10). Normal males do not have any

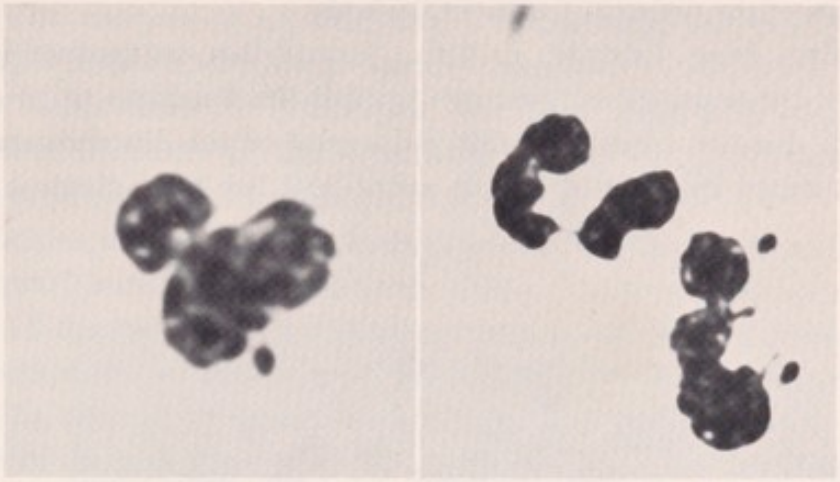

Fig. 2-10. A, Typical drumstick in polymorphonuclear leukocyte found in a normal female. **B,** Neutrophil with two drumsticks found in blood film of female with a triple X sex chromosome constitution.

drumsticks. The female drumstick also seems to be similarly related to the inactivated X chromosome.

At the present time nuclear sex determination is a valuable adjunct to the complete cytogenetic analyses in individuals, and, certainly, is useful as a screening agent in large population studies. The sex chromatin test is especially useful in the determination of sex in newborn infants with ambiguous or abnormal genitalia, and in screening newborn populations for sex anomalies. The sex chromatin pattern is an essential part of the work-up of any adult with a fertility problem. As we will indicate later in our discussion of sex abnormalities, a sex chromatin test should also be employed for those children with low birth weights (indicative of Turner's syndrome), young girls with hernias (indicative of testicular feminization), and young boys with mental retardation (indicative of Klinefelter's syndrome).

CHROMOSOME ANALYSIS

Each cell in the body (including the original fertilized egg) contains 100,000 or so genes. These genes or minute units of deoxyribonucleic acid (DNA) are arranged in linear fashion on the chromosomes. The chromosomes (Greek for "colored bodies") themselves are visible, with the aid of stains, in the nuclei of cells during the mitotic phase of the cell division. It was only recently, however, that, through the use of new techniques of tissue culture and cytogenetic analysis, routine examination of the human chromosome complement became practical (and accurate). Because of poor methodology, most of the investigators involved in counting human chromosomes for many years had arrived at the incorrect chromosome number of 48. We imagine that many of the biology textbooks on high school library bookshelves may contain this inaccuracy, since it was as recently as 1956 that Tjio and Levan established that the diploid number of

chromosomes in man is 46. The finding of 46 chromosomes is remarkably constant in cells of the different tissues in the body.

Several years later, Lejeune, in turn, showed that mongolism is due to an abnormality in chromosome number and opened the floodgate to an ever increasing number of diseases associated with autosomal or sex chromosome anomalies. It is now estimated that about one in every 150 live-born children has a gross

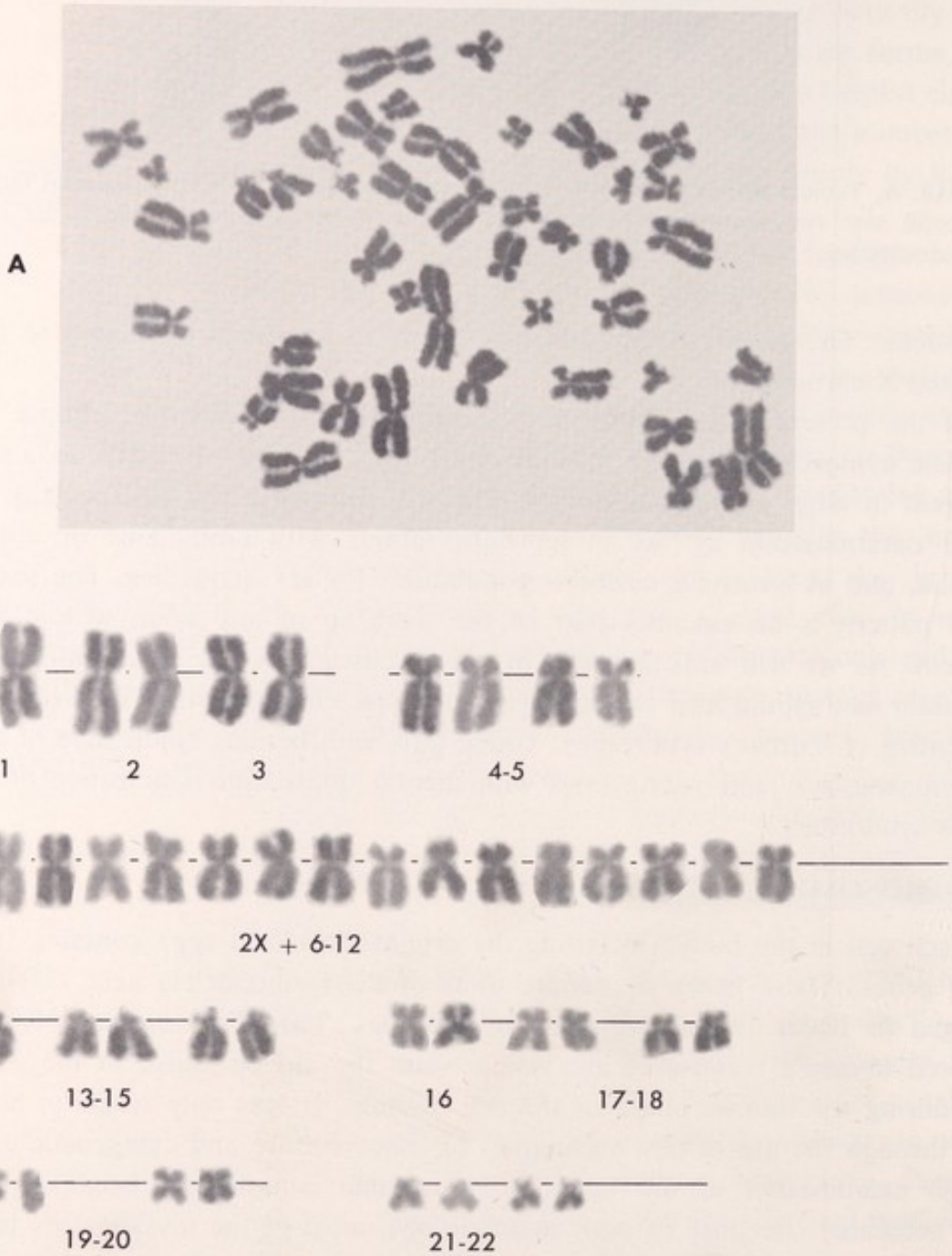

Fig. 2-11. A, A "metaphase figure" from peripheral blood cultures. The chromosomes are enlarged about 2,000 times. **B,** Normal female karyotype. **C,** Normal male karyotype. Karyotypes are prepared according to the Chicago Conference on Standardization of Human Cytogenetics, September, 1966.

chromosomal defect, either in the number of the chromosomes or in their morphology. The analysis of an individual's chromosome makeup has thus assumed great clinical importance. Since the chromosomes are crowded with the genetic factors of inheritance, it is obvious that even apparently small alterations in chromosomal structure, or duplications or deficiencies in chromosomal material, can cause profound abnormalities in the individual.

Innovations in tissue culture and cytogenetic technique led to the establishment of a "normal" human karyotype (Fig. 2-11). These innovations included the following: (1) the use of mitotic poisons, such as colchicine, which arrest cell division at metaphase, so that a great number of cells of any one individual can be studied; (2) the use of hypotonic solutions that cause swelling of the cells and separation of chromosomes from the tangle of the spindle body so that they can be counted; and (3) "squashing" or air-drying the preparations on slides so that the chromosomes are spread out in the same optical plane.

Obviously the most readily accessible and thus most useful source of cells for chromosomal analysis is the peripheral blood. The lymphocyte cells in the blood are stimulated to divide by phytohemagglutinin—a plant extract derived from *Phaseolus vulgaris,* the red kidney bean. In about 48 to 72 hours, the small lymphocytes, which ordinarily may spend up to several years in the circulation without dividing, are transformed into large "blastlike cells," which then undergo mitosis. Since the same transformation of lymphocytes into mitotically active cells can be effected by the use of certain antigens in cultures of cells from sensitive individuals (for example, tuberculin in peripheral blood cultures of positive tuber-

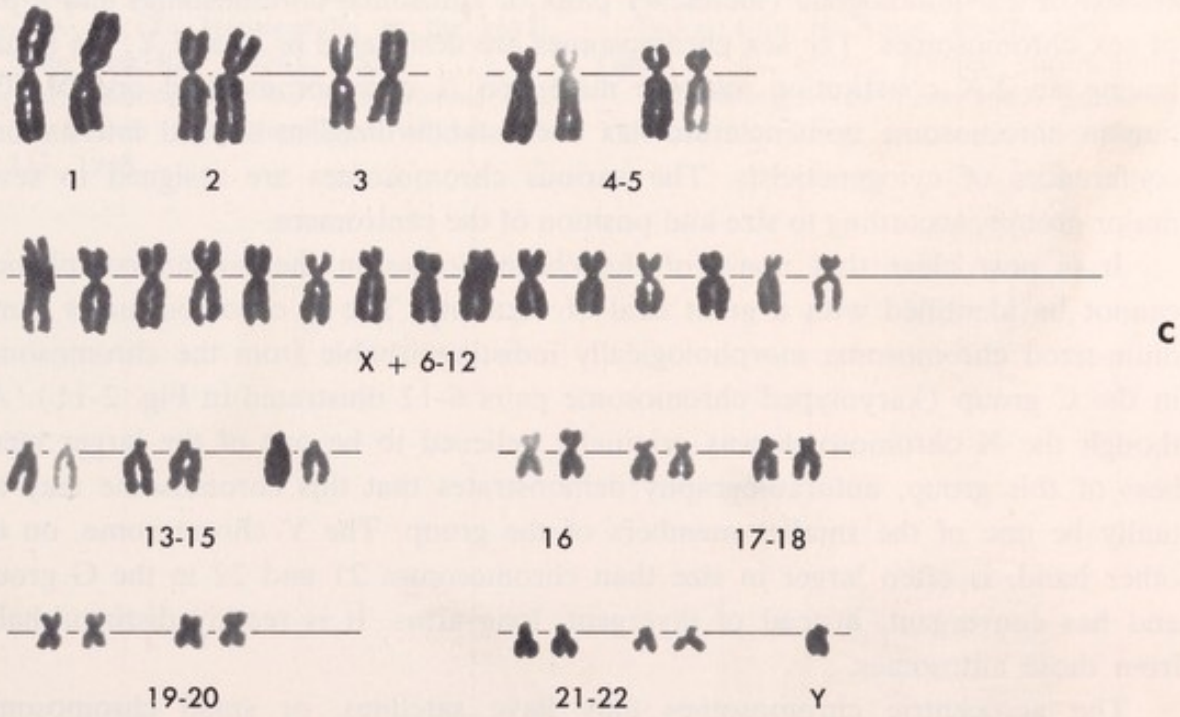

Fig. 2-11, cont'd. For legend see opposite page.

culin skin reactors), the phenomenon may represent an immune or antigen-antibody reaction.

Bone marrow, which has a great number of spontaneously and rapidly dividing cells, may be a good source for chromosome analysis in certain cases. Small skin biopsies may also be utilized when the examination of several tissues (such as in possible mosaic individuals) seems warranted. But fibroblast cultures (derived from the original skin fragment explant) generally require a tissue culture facility, because the cells must be cultured up to several weeks.

THE KARYOTYPE

The determination of an individual's karyotype involves counting the chromosomes in a number of cells and then analyzing these cells in detail. The chromosomes are generally counted with the aid of an oil immersion objective of a light microscope (×970). The largest of the chromosomes are about 7μ or 8μ in size. Generally, utilizing photographic technique (although some workers employ camera lucida drawings), enlargements of the chromosome metaphase figures can be made. At metaphase, the chromosomes are composed of two longitudinal identical halves (chromatids), united at a central constriction called the centromere. The identification of the individual chromosomes depends basically on two features: the total length of the arms of the chromosomes and the relative position of the centromere. Chromosomes are described as *metacentric* when the centromere is at a median position, so that both arms, as they are called, are of equal length; *acrocentric,* when the centromere is almost at the terminal point of the chromosome, and one of the arms is very short; and *submetacentric,* when the centromere lies between these two points. The 46 chromosomes of the human complement consist of 22 homologous (identical) pairs of autosomal chromosomes and a pair of sex chromosomes. The sex chromosomes are designated as X and Y, the female having an XX constitution and the male one X chromosome and one Y. The human chromosome nomenclature has been standardized at several international conferences of cytogeneticists. The various chromosomes are assigned to seven major groups, according to size and position of the centromere.

It is now clear that many of the chromosomes in the human complement cannot be identified with a great deal of certainty. The X chromosome is a medium-sized chromosome morphologically indistinguishable from the chromosomes in the C group (karyotyped chromosome pairs 6-12 illustrated in Fig. 2-11). Although the X chromosome was originally believed to be one of the larger members of this group, autoradiography demonstrates that this chromosome may actually be one of the smaller members of the group. The Y chromosome, on the other hand, is often larger in size than chromosomes 21 and 22 in the G group, and has convergent, instead of divergent, long arms. It is readily distinguishable from those autosomes.

The acrocentric chromosomes may have satellites, or small chromosomal masses connected to the main chromatid body by a very fine strand of chromatin.

The role of satellites in the causation of chromosomal abnormalities remains uncertain. Presence of enlarged satellites apparently may be a familial trait.

A relatively new technique that does permit definitive identification of certain individual chromosomes is autoradiography. Utilizing tritiated (H_3) thymidine, the replication patterns of several of the autosomal chromosomes and one of the X chromosomes may be differentiated from those of the other chromosomes.

When the chromosomes of the individual have been karyotyped, abnormalities involving chromosome number and structure can be detected. The many types of chromosomal anomalies that are associated with malformations in man will be discussed in the following chapters.

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Chapter 3

A general approach to genetic counseling

Counseling about genetic disorders is the last "procedure" to be considered in the practical application of medical genetics. Prior to this step, the physician has gathered before him an array of familial, clinical, and laboratory data that have led to his diagnosis. Also, the physician has, or should have, availed himself of additional information from a review of the literature about the disease. Now, all of the information derived from the previous procedures is to be given to the interested parties: parents, couples seeking advice prior to marriage, adoptive parents, or, sometimes, the patient himself.

Variations in the classes of recipients, variations in the psychological makeup of people who constitute these classes, and variations in the nature of the information to be given by the physician create complexities for counseling. Such complexities cannot be dispelled by cookbook approaches or pat procedures on the physician's part. Counseling, it is often said, is an art—and, as in many other arts, there are no exact formulas for performing it well. Personal judgment springing from experience governs much of the physician's approach. He, too, like his recipients, is subject to psychological factors that are likely to affect his counseling.

That counseling is complex does not mean to us, however, that any approaches taken by the physician are equally permissible or equally effective. Nor do we believe that the complexities of the counseling situation present insurmountable obstacles to giving good advice well. We will try to provide, in this chapter, some broad guidelines that physicians may consider in order to make counseling less complex and more effective. Specificially we will discuss who should give counseling information, when counseling should be done, what information should be given in counseling, and how this information should be given.

THE COUNSELOR

The person who gives genetic information or advice is most often a physician, by virtue of the fact that genetic disorders are medical problems. Frequently, genetic advice is given by a physician who specializes in dealing with the major systems affected by the genetic disorder. Genetic counseling about chromosome

disorders is likely to be done by physicians interested in mental retardation; genetic counseling about hemolytic disorders is likely to be done by a hematologist, and genetic counseling about some birth defects may be done by a pediatrician.

The family physician, in the form of a general practitioner, comes in for his share of counseling, too. In rural areas and small towns, he may be the first and only resource for giving genetic advice to all types of patients. In other locales he may be the first person who detects the "funny looking kid" or the child with a birth defect and, consequently, institutes the referral to a specialty center.

A final source of medically oriented counselors is the person who is called a medical geneticist or genetic counselor. Usually he has become a specialist in this field by peripheral means. He may have been a specialist in cardiology, anatomy, hematology, or some other field and then "wandered," by interest or accident, into genetics and genetic counseling. These specialists, obviously, occupy themselves directly with diagnosing genetic disorders and giving genetic advice.

Genetic counselors not obtained from the medical ranks are also found in health-related professions. Genetic advice is sometimes given by guidance counselors, family counselors, and public heath nurses. In some rare instances, genetic counselors have been Ph.D.'s who have come from the field of cytogenetics or some allied disciplines.

The emergence of genetic counselors from a number of disciplines must be viewed with mixed feelings. To be sure, the manpower needs for this activity are such that we must use people where we can find them. The trouble with the diversity in counselors' backgrounds is that counseling preserves tend to become balkanized and are jealously guarded. For example, the physician who treats fibrocystic disease tends to prohibit from counseling "his" family any professional who does not carry the same credentials as the physician's. Professional counselors likewise tend to erect fences around their area of counseling interest and, by fiat, allow other professionals to give genetic facts but not counseling. In all such instances, the patient's family may be shunted from one professional to another, each of whom gives some advice in terms of his specialty. The family may receive the sum total of the pertinent information, but only in a piecemeal fashion. One can easily imagine how confusing genetic information can be when given in this way.

Counseling preserves established by vested areas of interest also increase the likelihood that families will miss vital pieces of information. When no one person carries the primary responsibility for organizing the genetic information and counseling the family, important aspects of information may be overlooked. Each professional in the chain of referrals may think that someone else has, or should have, dealt with a certain topic.

Consider the case of the family who came to the birth defects center with an almost helpless young child found to be profoundly retarded. The previous medical contacts made by this family on the child's behalf had consisted of numerous visits to the family pediatrician and to various specialists, including an orthopedist,

a general surgeon, and an allergist. Prior to the family's visit to the center, medical attention had apparently been paid mostly to the surgical removal of extra digits on the child's hands and feet. The family had finally come to the center because it had become obvious that the child's progress was markedly delayed—yet in all those numerous visits to different physicians, the parents had never been told that their child was profoundly retarded or that there might be a genetic problem involved, despite the fact that such a condition was obvious from birth. In fact, the child was found to have a translocation type of D-trisomy abnormality, and the father to be the carrier of the abnormal translocation chromosome. Imagine the spiritual as well as the economic bankruptcy of this family by the time they learned that the surgical procedures had not much more than cosmetic value, and that much more serious problems were involved.

Many of us have probably had the experience of seeing families who may be aware of the mental retardation of their children but who have little or no information about the genetic factors that may be involved. Even when the disease condition appears obvious, such as in Down's syndrome, vital information may be unsought or unexplained by the numerous professionals seen by the family. Some mongoloid children have been diagnosed as having the 21-trisomy form of Down's syndrome on the basis of physical stigmata alone. Unless chromosome analysis is performed, genetic counseling may be misinformative, as the child may have a translocation or mosaic form of mongolism. The translocation form carries different genetic risks for recurrence, and the mosaic chromosome constitution has different intellectual and physical sequelae, as you will see in Chapter 6.

In view of the preceding discussion, the question of who should conduct genetic counseling is not an easy one to answer. We see no reason to limit the role to any one profession, particularly since to do so would decrease the amount of counseling available in the face of a rising demand for such counseling. We do see a need, however, to limit the genetic counseling of a particular family to as few professionals as possible. It does not appear psychologically wise (or economical) for families to have counseling gerrymandered into a number of genetically related aspects, each with its own information, its own specialist, and its own frame of reference.

The ideal genetic counselor is that professional who assumes the obligations of learning the general workings of heredity, organizing the pertinent sources of information for a genetic problem, exercising an "art" for giving that information properly, and helping to develop a program of action for families to follow. Whatever his professional title, a genetic counselor is the one who takes on those obligations. As we will indicate many times in this book, one does not have to be a geneticist to be a good genetic counselor.

COUNSELING TIMING

Genetic counseling should be considered when a genetic question has been raised. Genetic counseling should be carried out when the counselor has the rele-

vant information and advice available for answering that question. This would appear to be a simple answer to the question of when one should counsel.

The time for genetic counseling, however, does present some problems in view of our previous examination of the process by which some families go from one professional to another. As we said before, the multireferral system seems to promote the families' sequential acquisition of bits and pieces of genetically related advice, without permitting these families to partake of an organized and comprehensive counseling session per se. Often, when the families put the bits and pieces of information together, they counsel themselves. For these families, and for those who receive bona fide genetic counseling terminal to all other kinds of "counseling" sessions, the ideal time for genetic counseling has been missed.

The genetic counselor who faces a family that has been seen by many persons and many agencies over a period of time has the formidable task of trying to integrate his information with that which the family already, often perplexedly, holds. The counselor may have to unwind and sort out some families' entangled and confused conceptions of previously gained information. Sometimes he may have the more unpleasant duty of trying to undo misinformation and bad advice previously given. Add to these difficulties his task of trying to offset the effects on families of old wives' tales, superstitions, and "facts" gleaned from relatives, neighbors, and friends, and we can see how difficult it is to conduct genetic counseling long after the genetic disorder has been detected.

As an example, a family recently brought to the birth defects center an adopted son with a 6-year history of medical attention for a cleft palate, cleft lip (which was being repaired), undescended testes, and a number of other physical and intellectual anomalies. The parents had received much advice from physicians, some of which had been grossly misleading in encouraging the parents to believe the boy would "grow out of it." In addition, little or no attention had been paid to the disturbed family situation, which, it was found, stemmed from the fact that the adopted boy was the illegitimate child of a teen-age daughter in the family. Surely, early genetic counseling not only would have touched upon the genetic problem itself but also would have helped these parents to understand the difficulties of raising the daughter's child as if he were her brother. In this case, and with little qualification, in most cases, the time for genetic counseling should be considered with the thought in mind, "the sooner the better."

The genetic counselor does not always see families who have an extensive history of being counseled about a genetic affliction. Genetic problems that arise de novo, such as the congenital malformations detected in the hospital nursery, can be approached with thoughtful planning about the time for counseling. In these cases, the hospital personnel coming into contact with the parents should be considered part of the counseling "team," since they, by word or gesture, may give the parents information. Hospital personnel should be told when the parents are to be counseled, and it may be appropriate to tell them what information will be related in counseling. In this way the nurses, residents, and other staff members can govern

their interactions with the parents so that inappropriate disclosures of information (or misinformation) can be avoided.

Another, and in many cases the most important, reason for making genetic advice available as soon as possible is that couples can be given the opportunity to govern their family size. Genetic advice given after the mother is pregnant again, or after a family has had several children subsequent to the afflicted child, is a poor form of positive eugenics. Often this situation is unavoidable because the disease becomes known only by its occurrence in several family members. Moreover, diseases with manifestations later in life, such as Huntington's chorea, do not enable us to give advice before the size of the immediate family is achieved. Yet we all know of families in which several children had been afflicted by fibrocystic disease, albinism, phenylketonuria, or some other condition before genetic advice was given.

Most genetic counseling occurs "after the fact." For the reasons discussed previously, this is not the ideal time for giving advice. Despite the suitability of timing counseling to occur "before the fact," such counseling is rare. The exceptions—premarital counseling or, in some instances, preadoptive counseling—do provide us with the most opportune times to give genetic advice. Many times, however, we can give little advice to these persons because, unless a genetic disorder is already manifested somewhere in the families, we know nothing about the disorders possible. Few carriers of genetic diseases are capable of being detected by any means prior to the occurrence of the disease.

So, the ideal time for counseling is the time when our ignorance is likely to be most pronounced. It is unfortunate that families and physicians alike usually can raise genetic questions only when there are genetic problems. For the families' sake, one can hope that the questions are asked and answered as soon as possible.

COUNSELING CONTENT AND STRATEGY

Genetic counseling stresses genetic information: diagnosis, prognosis, presentation of odds for recurrence, and the effect of genetic diseases on the family. The delivery of that information is central to what the genetic counselor's task is considered to be. What that information should include and how one might deliver it are questions germane to this section and to most of this book.

The delivery of information, genetic or otherwise, is a communication task. The counselor, or communicator, seeks to transmit information to a receiver, in such a way that difficulties ("static") resulting from the communication process do not produce deterioration of the message's content. Effective communication is judged by the recipient's appropriate reception, understanding, and action based on the information imparted. It is the counselor's role to promote effective communication—a role for which most physicians have unfortunately had little training.

Genetic counseling, in terms of communication, is not unlike other forms of

counseling. It has its psychological or psychiatric considerations; it involves semantics; it touches on values and beliefs within the constraints of realism; it is (or should be) personal. The counselor's approaches to communication are critical: they must be persuasive without offending; they must be based on authority without being authoritarian; they must be directive without excluding freedom of choice. The counselor himself should be knowledgeable about genetics, sensitive to people, flexible in his approach, and humane. As for the couples, the families, the patients, there can be no "oughts" or "shoulds"; we have to take them as we find them—as people seriously in need of help.

As we stated earlier, many families seen by a genetic counselor have some sort of medical history involving counseling antecedent to the present counselor's contact with the family. Counseling may start by ascertaining what that history has been. The counselor can find out where the parents have been, what procedures were carried out, and what they were told. In this way, he can judge the extent to which the parents have developed an inventory of "facts" and plans concerning their genetic disorder. Some genetic counseling units, birth defects centers, and similar groups obtain this type of information prior to counseling and thereby save counseling time for delivering, rather than eliciting, information.

The counselor should view all of this information recited by the parents as a type of "truth" as they know it, whether or not what the parents relate fits the medical facts known by the counselor. Apparent discrepancies between what the parents relate and what is, or should be, medically true may be indicative of "defense" mechanisms employed by the parents; but it is more likely that these discrepancies or distortions are due to poor medical communication that has occurred in the past. Imagine the distortions or "static" that must ensue when unsophisticated parents are given medical information infiltrated with medical terminology. Add to these distortions the distortions resulting from the vague manner in which some counselors express themselves, plus their reluctance to discuss some areas at all, and it is small wonder that some parents relate a jumble of peculiar "facts" given to them in the past.

An additional advantage of eliciting previously gained information from the parents is that the counselor can determine how receptive the parents will be to his counseling. What the parents say and how they say it will tell him much about their intellectual understanding and emotional acceptance of the medical advice to be offered. The parents who tell of their having been to other centers, indicate that they have been told about the genetic problem, the physical or mental defects involved, and recite the odds for recurrence, all with accuracy, are obviously knowledgeable and should be easy to counsel. But if they relate accurate information with disbelief, it is equally obvious that they know about the problem but may not accept what they know. In this case the counselor's job is going to be more difficult, and his counseling may demand a different type of strategy. Conversely, parents who seem to know very little after having been to many physicians and specialty centers may have lacked the ability to understand what they

were told, or they may have been poorly counseled. The counselor should be sensitive to the origin of the difficulties.

It is also useful to find out what the parents have done on the basis of the previous information given them. The realistic orientation of a family can be assessed by determining how appropriately they have used opportunities to carry out actions based on information and advice given them previously. Again, we must be careful to match what the parents have done with what they had been told. Inappropriate actions may have been undertaken by the parents because they were given poor advice or they were given advice poorly. As in all other aspects of the counselor's "sizing-up" of the parents, it is the counselor's burden to determine which is the case.

For all families, and particularly for those who have not had a prior history of being given advice, it is important for the counselor to place the present diagnosis within the context of a review of the patient's history. This historical review can include the medical history gained from the family, a résumé of the family pedigree, if appropriate, and a review of the clinical procedures that have led up to the counseling session. Even though the family may have been told before about the use of clinical tools, it is important to refresh their memories so that the diagnostic information is made immediately relevant.

After his reviews of the medical history and the clinical procedures, the counselor is ready to give the diagnostic findings. This step presupposes that the counselor has ascertained that the parents are receptive. Most parents will be. In some cases, however, the counselor may have determined from the parent's behavior that he is not "getting across." He may then wish to alter his strategy from one by which he proceeds directly to the diagnosis to one by which he explores those factors that may be causing difficulties in communication. The counselor can spend more time reviewing the history, the parents' difficulties in the past, and their feelings about all that has happened to them. Even in one session, by being given time to ventilate their feelings to a patient and sympathetic ear, parents can better listen to the counselor. Sometimes, the counselor may find that all he has to do is simplify his explanation of the problem. In our experience such strategies are usually unnecessary; the counselor can proceed directly to his diagnosis.

Giving the diagnosis is quite likely to be the most difficult part of the communication process because some diagnostic terms are so commonly known that their mere mention may evoke fearful reactions from counselors and families alike. A diagnosis per se is nothing more than a label attached to a physical condition. It is what the diagnosis *means* that is important to the counselor and the family. For the counselor, the meaning of the diagnosis is self-evident. He knows how grave the problem is because he knows how bleak the therapeutic outlook is for most of the genetic diseases. For the family, similar, partial, or even mistaken knowledge about genetic diseases evokes the same grave concern. Some of the genetic disorders described in this book are so commonly known that their mere mention is prognostically as well as diagnostically informative to many, even unsophisticated, persons.

The counselor's knowledge about the disease may cause him great difficulties in giving the diagnosis. He may experience extreme emotional upheavals and, in order to control these feelings, employ defense mechanisms similar to those attributed to some parents. He may avoid or deny the clinical importance of giving a family genetic advice. In some cases he may delay giving the bad news so that some other professional will be given the task. The counselor who is the family physician is particularly subject to these emotional difficulties. It is not uncommon for him to refer a family to a specialty center because the professionals there will inform the family of a diagnosis that he has already made. One cannot prohibit such reactions in counselors any more than one can prohibit them in other people; yet if counselors are to communicate effectively, they must avoid letting these reactions affect their attitudes toward counseling and their behavior toward the family.

The penalties for the counselor's difficulties in imparting the diagnosis are most likely to be penalties for the family rather than for the counselor. Parents who are sent around from one physician to another, so that someone else will "do the dirty work," may later be accused by professionals of "shopping around." They will receive increasingly negative treatment by professionals contacted in the future, who view all of the referrals not as a result of poor counseling but as a case of unrealistic parents. In other cases, the counseling physician may actually give the diagnosis but only in a cold, blunt, or "quick-kill" fashion. Such a counselor need not be a heartless man; on the contrary, he may be so upset about what he must relate that he has to "get it over with" in a hurry. Again, such difficulties in a counselor produce cruel repercussions for the parents. Another counselor may spend great amounts of time talking around the point, avoiding the issue until, in some cases, the parents themselves pronounce the diagnosis. What a relief for him! What an excruciating ordeal for those parents.

The excuses offered by professionals for inadequate approaches to giving families diagnostic information are monotonously predictable: "people don't want to hear the truth"; "people won't believe what we tell them anyway"; "you have to shock some people to get them to listen to you"; "all people have such guilt complexes about these problems that they will deny our diagnosis." The small number of people for whom these statements are appropriate hardly justify the shopworn claims of validity for such excuses. If the counselor avoids the situation by his hasty or tardy remarks, the parents are tacitly given professional permission to do the same thing. The counselor who conveys the impression that he cannot cope with the *fact* of a genetic disease is not likely to convey the assurance that a family should be able to cope with the consequences of a genetic disease.

The content that the counselor offers in his diagnosis may be supplemented by explanations of how such a diagnosis was reached. The counselor has already indicated what the clinical procedures were; now he can show the relevance of particular findings to his diagnosis. In counseling many parents, the counselor may find it useful to show a karyotype or some similar evidence of positive clinical results. When the patient displays the phenotypic expression of a genetic dis-

ease, the counselor can show the parents a photograph that the literature gives as the classic expression of the disease. Some photographs included in this book can be used for that purpose.

Along with the diagnosis, the important information to be given by the counselor is the prognosis, under which we will include the risks for the recurrence of the genetic disease in other offspring and the consequences that the disease holds for the afflicted family member. In many counseling sessions, this may be the most difficult material for the counselor to impart, because this information carries the practical significance of the diagnosis.

We have always considered it a good strategy to spell out the consequences of the genetic disease for the patient before indicating the risks for the recurrence of the disease in future offspring. We may vary this strategy to fit a particular disease in question, but, for most genetic diseases, this approach to counseling enables us to make sure that the family has a chance to understand the significance of the disease diagnosed. The risk figures attached to genetic disorders are not very meaningful unless the family is aware of the penalty for taking the risk and perhaps losing. What the family loses is clarified by explaining what the consequences of the disease are.

The problems in giving families information about the prognosis of a genetic disease are, for the counselor, essentially like the problems he has in giving the diagnosis. Again, his emotional adjustment to the counseling burden has to be considered for effective counseling to take place. Honesty and an accurate appraisal of the consequences of the disease are called for. Evasion of the truth is likely to occur at this time and can be very harmful. It is remarkable to see how many times parents are told what genetic disease their child has, and yet are given little or no indication of the prognosis. To be sure, this may result from ignorance on the part of a counselor. Too often, however, a counselor simply does not have the security to tell parents about the realities of the disease.

A family recently came to us with an infant about 1 year of age. They were quite aware that he had suffered some effects from kernicterus due to Rh incompatibility, and they were aware of the genetic aspects of this condition. The parents, who were quite intelligent, sounded almost like textbooks in describing the diagnosis—yet they had been given almost no information about the consequences of this disease to their child until a few weeks prior to their visit to the genetic counseling clinic. In fact, up until that time, the parents had been led to believe that their child was doing well and that the few problems he had, such as difficulties in motor movements, would improve remarkably as he grew older. This was an absolute misstatement of the facts—the child was totally deaf and showed signs of extensive brain damage to motor and other areas. No one can guess exactly what the future holds for a child who is cerebrally palsied and deaf, but certainly he is not going to grow out of any of these difficulties.

The foregoing example should not suggest that giving an honest genetic progno-

sis always shatters parents' unrealistic hopes. In some cases, when the prognosis has been described inaccurately or not described at all, some parents have assumed the worst or given the child up for lost. What may be bad news for the counselor to give might be relatively good news to some parents.

The prognosis of many genetic diseases is often linked with limitations of the patient's life that are due to deficiencies in the patient's intelligence. Some of the genetic diseases mentioned in this book involve mental retardation as a concomitant to the disease. When the counselor gives information about these diseases, he must also counsel about the retardation. Other genetic diseases may not be related to retardation per se but may be manifested by isolable intellectual deficits. These deficits should be mentioned in counseling. Given thorough information regarding whatever intellectual handicaps may accompany the genetic disease, parents can learn what to expect from their child and can, with guidance, learn new management plans appropriate to their new expectations. For this reason, it is important that the counselor be as precise as possible in his description of the intellectual deficits, and that he avoid the comforting terms that are often so misleading.

A surprising number of counselors will avoid the term "mental retardation," let alone the qualifying terms for the degrees of retardation. The terms substituted for "mental retardation" include "slow," "late," and "behind," which, to many people, do not suggest retardation at all. Most parents have no conception of the meaning of such a phrase as "slow in developing," although this is the phrase most often used by physicians to indicate mental retardation. A slow child in school may still graduate from high school; the retarded child will not.

The use of vague terms by the genetic counselor may also be due to his difficulties in giving people bad news; but, as we know, the penalties for the counselor's self-comfort are manifested in those parents who continue to "shop" for useful information, set up the wrong child-rearing practices, and continue to "deny" the problem. The counselor must recognize that he supports or even promotes "denial," shopping, and poor management when he, for whatever reason, is imprecise in his counseling.

After the counselor has been assured that the parents are aware of the disease's consequences, he must introduce the available risk figures for recurrence of the genetic disorder. It is this information that will probably influence the parents' or blood relatives' eugenic considerations. The size of the immediate families involved and the future mating behavior and production of offspring among the children are likely to be governed by the determination of risk. Because of the importance of these risk figures, the counselor must be especially careful to make them as meaningful as possible. Unfortunately, the roulette-wheel characteristics of many risk figures do not allow the counselor's quoting of simple "odds" or "chances" to be very compelling unless the disease is serious and the risks are high. When the risks are low (less than one chance in four, let us say) and the disease is less serious, then the counselor may have to explore many avenues for getting the parents to appreciate what the risks really are. As in many other aspects

of genetic counseling, the counselor's obligation is to make sure that the parents understand what is being said. It is not enough for him to be satisfied with the fact that he has given the parents some numbers to play with.

The final specific area of content for the counselor to formulate concerns programs of action and sources of service that families have available to them. The counselor's guidance in helping the family to obtain appropriate therapeutic or supportive help from the community is perhaps one of the immediately positive aspects of counseling. Many good counseling sessions have been ruined by the counselor's being unprepared to give parents this kind of information. For parents who wish to have no more children for genetic reasons, counselors should be aware of the adoption agencies available and their current adoption procedures. The counselor also might explore the risks attached to adoptions and further indicate that he will be glad to give the parents additional advice when adoption is being undertaken. The counselor should know what residential institutions, special schools, and vocational programs are available. He should also find out what restrictions these services impose because of their waiting lists, costs, and requirements for admission. In some cases, family planning services, guidance counseling, and the resources of mental health agencies may be needed. Also, the counselor must be aware of religious aspects concerning family planning, adoption, and premarital advice, so that he can call upon, or encourage the family to call upon, clergymen for additional advice. Some of the genetic diseases call for medical management. The counselor should indicate why medical management is necessary and to whom the parents can turn for management. To give but two examples, the child with phenylketonuria can receive a special diet, and the child with a sex chromosome disorder can receive hormone therapy.

Finally, the counselor should extend to the family the ultimate resource he has available—his own continued interest in the family and his desire to provide them with advice in the future.

COUNSELING "STYLE"

The content of counseling information cannot be divorced from the counselor's approach or style in delivering that content. We all know from our own experience that one person can communicate more effectively than another, even though both may be using the same ideas or even the same words. A person's manner, looks, choice of words, and organization of ideas are but a few of the attributes that make for effective or ineffective communication. For the genetic counselor, these attributes come into play during counseling along with such other attributes as sensitivity, sincerity, honesty, flexibility, and a sense of timing for giving the important information at the right point in the counseling. These attributes make up the counselor's style or, to use an old medical term, "bedside manner." We do not believe that many of these attributes can be acquired by counselors through didactic methods. No one can impart or teach by some method a means for would-be counselors to become sincere, sensitive, or flexible—yet it does seem

possible that the genetic counselor, as a communicator, can be taught some effective approaches to counseling.

The effective counselor is the one who knows his information and is capable of communicating (or teaching) it to the family. He has relatively few ideas to get across to parents; these ideas should form the structure of his counseling. When we discussed the content of counseling, we outlined some of the broad aspects of these simple ideas. The delivery of these few ideas requires, as its top priority, honesty. The counselor should realize that no amount of sidestepping the honest delivery of these ideas will ever "cure" a genetic disease. Genetic disorders do not get better, no matter how much the counselor, for whatever reason, withholds from families the diagnostic aspects of those disorders. Nor will the counselor's "sins of omission" change the recurrence risks or alter many of the prognostic aspects of genetic diseases. Sooner or later, "nature will out."

Throughout his counseling, the effective counselor is the one who anticipates questions and areas of difficulty and conflict. The experienced counselor is likely to find this easy because, even with allowances for human individuality, his families will often show remarkable similarities. It is possible, therefore, for genetic advice and discussions to be conducted around anticipated central issues that the counselor can and should broach. For example, he should anticipate that among some families one spouse may blame the other for being the cause of the problem. This blame may be unexpressed by many parents. It is best for the counselor to open the topic by indicating that for most genetic disorders it usually takes both parents to bring about the display of the disease and, in any event, the capricious aspects of carrying deleterious genes are common to us all. If the counselor opens this topic to all parents, he runs no risk of upsetting those parents who have no resentment toward a spouse who is "to blame." For the others, he may be able to bring unexpressed resentment out into the open and alleviate some or all of the ill feeling.

There are many such themes and questions that can be anticipated and broached by the counselor. Some of these themes center around superstitions and prevailing myths in the community; others center around areas of ignorance common to families and, sometimes, medical personnel alike. In later chapters, we will introduce some of those themes appropriate to specific genetic disorders.

The reason for the counselor's anticipation and introduction of themes and questions in his counseling is that he cannot always be assured that these topics will come up spontaneously. We often assume that if people want to know something from their physician, they will ask. If they do not ask, we assume that they do not want to know or that they already know. We cannot make such assumptions in counseling families about genetics. We can assume that most parents will ask questions only by further assuming that they have enough knowledge about genetic diseases to formulate such questions. Most parents do not have that knowledge, but the counselor should. The counselor should both raise the questions and, if he can, answer them. Some parents will not ask questions because of

embarrassment, or because they are ashamed of some act that they may mistakenly believe to be related to their problem. For example, in one family with a defective firstborn male, we found that the parents believed that their child had a genetic disease because the boy had been conceived before they were married and they were being punished. A calculation of the child's age and their wedding date led us to anticipate that this might be an unvoiced concern. In general terms we opened the topic. It was at that point that the parents confirmed our hunch and, with relief, expressed feelings that they had harbored over several years.

As a final point, a counselor should try to develop critical insight into his own abilities for communicating effectively to people. The dictum "know thyself" is an important one for a genetic counselor. If giving honest, albeit disagreeable, information interferes with his counseling, or if he tries to muddle through counseling on the strength of his medical role, genetic counseling is not his game. In fact, it is one of the leitmotivs in this book that the role of genetic counselor is suited only to the person who places an emphasis on honest and effective communication. A counselor's analysis of his own capabilities may not make his communication more effective, but it can provide a starting point for improvement. Failing that, the counselor who is aware of his own shortcomings may persuade himself that some other occupation is more suited to his abilities.

Critical self-awareness on the counselor's part can help him to avoid ascribing to all parents the plethora of psychopathologic mechanisms that are said to beset people who have defective children. Much has been written about families with genetic problems who are laden with so much guilt and hostility that they deny their problems or regress to immature forms of behavior. No doubt all of us have counseled some families who have manifested these characteristics—yet it is our experience that most families do not display such disturbed forms of behavior when they receive accurate and useful advice through constructive counseling. This is not to say that these families have not been shaken by bad news; rather, it is to say that they have not been broken.

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Chapter 4

"Probabilities" in genetic counseling: the numbers game

Suppose a man tossing a dime said that he had tossed one hundred "heads" in a row and asked you what the next toss would be. You, as so many people, might be tempted to call the next toss "tails." The argument usually presented is that "tails" is about due to come up, or it is highly unlikely that you could get another "head" after having so many. In fact, however, the probability that a coin will come up "heads" again is the same probability as on the first, second, or any other toss. That probability is 0.50. No matter what the toss, if the coin is unbiased, the probability of an event "heads" is the same for each independent toss. The event that is unlikely, i.e., the event that has a low probability of happening, is the event of one hundred "heads" coming up in a row. One's best bet is that one hundred "heads" will not be tossed in a row. The poorer bet is that, after one hundred "heads," the next toss certainly should be "tails."

Most of us tend quite frequently to reason that independent events are somehow related. A baseball player who has a batting slump is said to be "due for a hit." Gambling tables are crowded with people who are trying to offset a "streak of bad luck" or continue to "ride a streak of good luck." This tendency is so common in gambling that it is called the "gambler's fallacy."

The connection between gambling and genetic counseling may appear to be tenuous, but the use or misuse of probability statements is common to both. Among some geneticists, genetic counseling consists only of playing the "numbers game." While we do not see genetic counseling only in that light, we realize that the combination of some rudimentary ideas of probability and some rudimentary principles of genetics will enable the physician to give advice in terms of "odds," "chances," or "probabilities" for many of the classic genetic conditions. For other genetically related conditions, the physician may not be certain of risk figures, but some numerical statement about the likelihood of the occurrence or repetition of the disorders is often possible.

We, as a people, believe in numbers. In discussing odds, the physician is not

likely to introduce a new concept to most citizens, since they receive the weather in terms of chances, know that their insurance premiums are based on odds, take chances on lotteries, and employ popular probability statements in everyday speech. That we are a numbers-conscious people, however, does not mean that we are enslaved by numbers. Couples seeking genetic advice have to hang the numbers onto something understandable. The physician is in a unique position to help them do just that. Of what use is a probability figure if a couple's appreciation of risk is different from that of the physician? People do vary in their subjective application of chances: some people bet only on sure things; others apparently take high risks, even when that risk involves having a defective child. Couples strongly desiring a child may consider a high risk worth the chance when faced with the childless alternative. In many cases, they undoubtedly believe that they can "beat the system." Couples who have had children may be quite likely to entertain a different set of subjective probabilities about the risks for genetic disorders. In these and similar instances, the physician, and especially the family physician, can utilize his knowledge about the family to enhance or qualify the dry risk figures given in textbooks. He knows the odds that will be useful to parents are the odds that parents customarily use. The physician realizes that giving medical advice means helping people to make *their* own decisions; he realizes that to help people means to give advice meaningfully. With this understanding, the following chapter will give some of the general rules by which numbers can be used in genetic counseling.

GARDEN PEA RULES

To Mendel, an Austrian monk living in the nineteenth century, goes most of the credit for laying the foundation of genetic mechanics. The happy combination of an intelligent monk with time on his hands, patches of garden peas, and some thoughtful hard work resulted in the rudimentary ideas that a physician giving genetic advice will find useful.

Mendel noticed that, among the garden peas, the ones with green seeds always bred true (i.e., they always had green seeds), and some yellow-seeded garden peas bred true and some did not. He took the green seeds that always bred true and crossed ("mated") them with only those yellow seeds that bred true. The first generation of plants was self-fertilized, and the seeds of the second generation were found to consist of yellow seeds and green seeds in the ratio of about 3:1. We can describe this event by the notation Y for the yellow seeds (Y is capitalized because it is dominant) and g for the green seeds. In the parent generation the union of YY and gg produced four possible combinations, all of which were Yg combinations. The self-fertilized second generation then had Yg and Yg combining, producing four possible offspring: YY, Yg, Yg, and gg. Since Y is dominant to g for showing the color trait, not only is YY yellow, but also Yg and Yg. The Yg's, however, will be carriers for the green trait. Only the combination gg can be seen as green. The green trait is called *recessive* because of its lack of phenotypic expression when the dominant Y is available.

For human genetics we can illustrate this "magic" 3:1 ratio by considering albinism, which is recessive to the normal gene of pigmentation. Following the example of the garden peas, we can expect the albino who marries a completely normal individual to have no albino offspring. However, one half of the offspring will be carriers of the abnormal gene for albinism. Now, if the carrier were to marry another carrier, then a random combination of the genes, on the average, would produce a predictable outcome if there were four children. We would expect one genotypically and phenotypically normal child, two phenotypically normal children (but who are carriers), and one albino. The ratio of normal-appearing children to the albino child is 3:1. Symbolically, this can be shown by letting *N* stand for the normal pigmentation trait and *a* stand for albinism. The normal, *NN,* who marries an albino, *aa,* will have all *Na* offspring. If the *Na* marries an *Na,* then, in four chldren, we would expect *NN, Na, Na,* and *aa.* The reader can easily see that if an albino, *aa,* marries an albino, *aa,* all children will be albinos. If a carrier, *Na,* marries an albino, *aa,* half of the children will be albinos and the other half will be phenotypically normal, but carriers. Here we have the ratio 1:1.

The ratio of 1:1 is a useful one to remember for dominant genetic disorders. For those disorders in which the harmful gene is dominant—such as Huntington's chorea or achondroplasia—on the average, half of the offspring in the first generation will manifest the disease; and in the next and following generations, half of those offspring will manifest the disease. The offspring who are phenotypically normal will also be genotypically normal.

The 3:1 ratio is also applicable to such cases as Huntington's chorea when both parents are afflicted with the disease. In this event three out of four children will have the disease. Fortunately, the incidence of the disease in the general population is quite low (1 out of about 25,000); therefore, the random mating of two people with the disease is very unlikely.

The two ratios, 3:1 and 1:1, may prove to be misleading if they are applied to an individual family exactly as given in the examples. These ratios represent averages for many families. The appropriate application of the ratio is for the likelihood of *each* child's having the particular trait involved. The genetic theory does not specify the characteristics of a particular child; it specifies the risks, on the average, that the characteristics will occur in any child—like our coin, the introduction of each child in an *independent* event. What this means for the physician in counseling is that he must not commit the "gambler's fallacy" at the family's expense. If a normal-appearing couple's first child is an albino, and the 3:1 ratio holds, the odds that the next child will be an albino are 1 out of 4. These odds hold for each subsequent child, regardless of the number of affected children. The physician would be ill-advised to tell the parents that once they have had an albino child, the other children will be or are likely to be normal. In those cases in which the genetic ratio of a disorder is 1:1, it is even more critical for the physician to make the odds clear to the parents.

ACTUARIAL RULES

Most of the better-known genetic disorders reported in the literature involve Mendelian rules of inheritance. Odds related to genetic disorders involving autosomal-dominant or recessive inheritance and X-linked inheritance are most easily explained in terms of these rules. If there are no genetic complications, such as might result from a mutation, these disorders seldom raise problems for counseling about further risk. In many other conditions, however, genetics appear to be involved, but not in such a clear-cut manner. Here the genetic counselor has to rely on a different set of "odds" or "chances" to give to the parents. When no definite pattern of inheritance can be traced, *empiric* risk figures indicate that heredity plays a role. These risk figures are obtained in basically the same manner that insurance companies originally derived their actuarial tables: by making a survey. The problem with this approach is that, unlike the population surveyed by insurance companies, populations in genetic surveys are usually quite small. The risk figures, therefore, are subject to considerable error. The physician will often be aware of the limitations of these surveys—yet at the present time, he can hardly ignore them for giving genetic advice. They may be poor guides, but they are the best guides available.

The application of empiric risk figures is relatively straightforward. How the physician interprets risk figures to the parents demands judicious consideration. When a normal couple has a child with a cleft lip (harelip), the risk to any subsequent child ranges from 4% to 7%. If the physician gave the risk figures in just that way, to some parents the risk might not sound so bad. If he went on to say that the incidence of cleft lip in the birth population is 1 per 1,000 births, and the parents' risk for another child with a cleft lip is 40 to 70 per 1,000, then the physician would present a more compelling set of figures. But if he gave the same information by saying that the couple's chances of having another child with a cleft lip are *40 to 70 times higher* than those of a couple taken at random, then the parents are likely to see the situation as serious.

The important point made by this illustration is that counseling employing empiric risk figures permits some latitude for interpretation. Numbers are numbers, but the context in which they are presented is going to bias their usefulness no matter how objective the numbers appear.

The physician should be especially cautious when interpreting risk figures in terms of percent increase. One may see a typical misuse of this type of interpretation in some newspaper reports of crime figures. The report that the number of murders in Exogenous City (population: 400,000) this year increased 200% does not seem nearly so alarming when we know that there was only one murder last year and this year there were three.

The interpretation of empiric risks demands the additional consideration that a random pregnancy may produce some serious abnormality. Some authorities place the chance of any pregnancy having any abnormal consequence at about 1 in 40. This risk figure does not apply to a specific disorder, but to any disorder. Parents

may view this as an alarming risk figure in itself. Apparently, though, most of us who are cognizant of this figure do not consider it so high a risk that we believe people should stop having children. Physicians should not, however, offset the weight of empiric risk figures for a given disorder by piecemeal comparisons with risk figures for all disorders. To many parents, a chance of 1 out of 40 for any disorder may not appear appreciably different from a chance of 1 out of 20 for the repetition of a given disorder. But if we assume that the occurrence of any disorder and the occurrence of a repetition of a disorder are independent events, the combined chance of having one condition (any disorder) or the other (the repetition) is about 1 out of 10. In fact, this assumption is untenable because the two events are not independent, since the recurrence of the specific disorder contributes to the total risk. Thus the combined risk figure is obviously going to be an overestimate—yet the assumption is of practical usefulness because it does highlight the increased risks.

A similar situation occurs when a mother over the age of 30 has a mongoloid child. The typical counseling approach is to advise her of the increased risk for having another mongoloid child. What is seldom explained to the mother is that she faces an increased risk for having a child with a number of other conditions, including spina bifida, hydrocephalus, cleft palate, and cleft lip. The combined risk figure for having another child with *any* affliction is appreciably higher than the risk figure for having another child with Down's syndrome.

The foregoing argument is not presented so that physicians can force a decision upon parents once they have had an afflicted child. Empiric risk figures, whether interpreted as high or low by a physician's judgment, are subjectively interpreted again by parents. The physician's job in giving risk figures is to present the figures in the context of total risk possibilities. The penalties for the potential child and family are too great for him to err in the direction of optimistic number-juggling.

RELATIVES AND THE BROTHERHOOD OF MAN

Previously, our discussions of numbers as applied to genetic events led us to simplify three primary risk indices: the 1:1 ratio for odds related to dominant inheritance, the 3:1 ratio for odds related to recessive inheritance, and empiric risk figures for the odds on a repetition of a genetic disorder. The situations in which the previous calculations of odds cannot be applied so simply are those involving multifactorial inheritance and inheritance from recessive genes available from common carriers in the population.

Multifactorial inheritance

Multifactorial or polygenic inheritance refers to genetic variations that are due to a number of genes held in common. This type of inheritance is difficult to evaluate genetically because the genetic variations do not follow simple Mendelian ratios, and each variation analyzed may be a very complex human characteristic—

e.g., intelligence. The concept "genes in common" typically refers to those genetic factors that have been acquired from an ancestor held in common. "Genes in common" can refer also, however, to those acquired from *a population* held in common. Genes are either alike or different; they do not respect family names or kinship systems. The reason that relatives and ancestors, instead of populations, are usually singled out for studying multifactorial inheritance is that relatives have an increased likelihood for possessing genes in common. This familial likelihood or chance for having genes in common provides the next set of numbers for the genetic counselor to keep in mind.

The simplest demonstration of genes in common may be found in the degree of some trait resemblance between relatives who vary in their degree of familial relationship. The degree of familial relationship is quantified genetically by stating the probability, on the average, that certain genes in common are present between two given relatives. The mathematics for developing these probabilities springs from the same approach we used in talking about coin tosses. Any parent gives to a child one or the other of the two alleles found at a locus on one of the chromosome pairs that he or she contributes to the child. In all cases, except those in which the alleles are X-linked or Y-linked, the child has received half of the total gene complement from one parent and half from the other. Therefore, the chances that a child will receive a particular allele carried by one parent but not by the other are one out of two. There is also a 50% chance that any two siblings will have received the same allele from the same parent. Half of the genes that are passed from the parent to the child are further halved when that child has a child. As the relationship between relatives becomes more distant, the proportion of genes in common clearly becomes less and less. Table 4-1 shows the relationship between different relatives and the percentage of genes expected, on the average, to be held in common.

The table represents a continuum of expected genetic commonality for which, in research, we would expect to have a correlative continuum of shared human traits. On genetic grounds alone, relatives who share some gene alleles should

Table 4-1. Genes in common as a function of familial relationship

Relation	*Expected probability (expressed as a fraction)*	*Expected percentage of genes in common*
Monozygotic twins	1	100
Parent to child	½	50
Dizygotic twins	½	50
Sib to sib	½	50
Grandparent to grandchild	¼	25
First cousins	⅛	12.5
Second cousins	1/32	3.125
Third cousins	1/128	0.781

show correlations greater than zero on a number of trait measurements. Indeed, this has been shown to be the case. Body weight and height, to mention but a few measurements, show correlations with magnitudes closely analogous to the proportions of genes expected in common.

Since the study of family pedigrees is a time-consuming procedure, most of the research on multifactorial inheritance has employed twins. So-called "twin studies," employing identical (monozygotic) and fraternal (dizygotic) twins, have done much to advance our understanding of relations between complex genetic factors and human attributes. Some of the interesting data from the studies of twins will be discussed later in the chapter on twins.

Consanguinity

Table 4-1, by inference, also helps one to see that when blood relatives marry, they increase their chances of accentuating polygenic factors. These factors may be beneficial or detrimental, depending on which ones are present. If the factors influence height or weight, it is not obvious that close inbreeding will be detrimental to environmental adaptation. Polygenic factors that may be related to intelligence, psychoses, neuroses, or mental retardation, for example, would, however, play a major role in environmental adaptation.

Apart from adaptation, mortality may be associated with polygenic factors and therefore can be influenced by consanguinity. In 1964, a World Health Organization report about child deaths in an American city indicated that the death rate for children of consanguineous marriages was between three and four times higher than the death rate in a comparison population. Despite the unknown environmental consequences of polygenic factors, the mortality rate alone would be enough to prohibit consanguinity.

The major reason for counseling against marriage between close relatives is not associated with polygenic inheritance, however. Prohibition of consanguineous marriages is usually, and rightfully, supported by the fact that offspring of these marriages are more likely to express deleterious recessive genes carried in the general population. The family member who carries a recessive gene is more likely to marry another carrier for that gene when he marries a close relative than when he marries some person from the population at large. The closer the relatives are to each other, the more likely it is that any gene will be held in common, recessive genes included.

Let us suppose that a man to be married is a carrier for cystic fibrosis. If he were to marry any unrelated person from the population at large, his chances of marrying another carrier are one in twenty-five. If he were to marry his first cousin, the chances of her being a carrier for cystic fibrosis are one in eight. The likelihood for the offspring of these first cousins to be homozygous for fibrocystic disease is about three times higher than if the heterozygote cousin married an unrelated person. Moreover, these same first cousins may share more than the recessive gene for cystic fibrosis. Since first cousins have one out of eight

of their genes in common, their offspring will be homozygous at one-sixteenth of *all* their gene loci.

The frequency of homozygosity may not be impressive when we consider all of the genes that are not detrimental to health and adaptation. But when we consider the frequency of concealed recessive genes carried by each of us, the relatively increased frequency of homozygosity for offspring of first cousins is of some consequence. It is estimated that each of us carries at least one deleterious recessive gene and three to eight deleterious mutations of specific genes; many of us carry more than this. Although the number of genetic disorders in the general population resulting from any of these specific recessive genes is not known, a conservative estimate would place the incidence as high as 2% of the birth population, or about 70,000 births per year.

Relatives with lesser degrees of consanguinity have, when they marry, decreased risk for producing offspring with rare recessive defects. Second cousins have 1/32 of their genes in common. Except when a known disorder is present in the family, there is not likely to be much concern from family or physician about marriages between second cousins. Nor do such marriages receive social opprobrium in the form of law. To take a conservative view, however, because of the increased risk, slight as it is, one might suggest that second cousins look elsewhere for marriage partners.

Other evidence for the effects of consanguinity upon the display of harmful recessive genes comes from studies on the incidence of consanguinity among parents of offspring showing a genetic disorder. Essentially, these studies are based on the principles that (1) parents of children showing a genetic anomaly are much more likely to be blood relatives than one would expect from random mating in the general population, and (2) the rarer a recessive condition is in the general population, the much more likely it is that its occurrence in an offspring is related to consanguinity.

Statistical application of these principles depends on two bits of information: the incidence of the recessive disorder in the general population and the average rate of consanguinity in the general population. In the United States, consanguinity involving first cousins is estimated to be, on the average, about 1% or less of total marriages contracted. This incidence, which is lower than that of most older countries, does not hold for cultural isolates such as the Amish group. If we compare the first-cousin–marriage incidence in the general population with that among parents of children with rare diseases, the results are striking. Table 4-2 shows the incidence of first cousin marriages for some recessive disorders.

In addition, we would expect from our principles of consanguinity that when the incidence of the trait (disease) in the general population is low, the number of first cousin marriages among the parents of children with genetic diseases is likely to be high. Although incidence figures are not available for all the recessive diseases, the figures available generally support our expectation. For example, Wilson's disease, an exceedingly rare disorder with an estimated incidence of

Table 4-2. First cousin marriages among parents of propositi with certain recessive traits

Trait	*Approximate incidence of first cousin marriages (percent)*
Infantile amaurotic idiocy	15-53
Wilson's disease	37-50
Alkaptonuria	30-40
Ichthyosis congenita	24-40
Xeroderma pigmentosum	20-26
Albinism	18-24
Total color blindness	11-21
Fibrocystic disease	Less than 5 (estimated)

one person out of a million, has a high consanguinity incidence. In contrast, fibrocystic disease is not an uncommon recessive disorder, and the consanguinity incidence is quite low. It must be remembered that the incidence figures are for the total population; subpopulation figures distort the apparent rarity of the disease. Infantile amaurotic idiocy is quite rare in the general population (accordingly, the consanguinity rates are high), but this disease is less rare among some Jewish subpopulations. Estimates of the incidence among these Jewish populations range from one afflicted child in 2,500 to one in 10,000 children.

Consanguinity among relatives more distant than first cousins is more common. The effect of marriage among more distant relatives is not clear, and the application of any analysis of consanguinity calls for a careful examination of the family pedigree. It is expected, however, that marriages of relatives other than first cousins are likely to manifest slightly higher rates of genetic disorders.

The evidence linking consanguinity and incidence of recessive diseases is compelling enough that marriages among first cousins appear unwise. One can easily translate the evidence given into terms of preventive medicine. If the marriages of first cousins had not occurred or if there had been no offspring from such marriages, the number of afflicted children among such families might have been reduced by about 10% to 50%! The physician can let first cousins contemplating marriage or having children interpret this information in their own way. Consideration of the family pedigrees showing a lack of abnormalities may offset the evidence; and, indeed, pedigrees should be considered. But, in any case, such considerations should be made in the context of available studies and the application of risk figures.

Population genetics

The preceding discussion of consanguinity was based on the concept of genes in common. The offspring of first cousins were said to be at higher risk for having a genetic disorder—not because the parents are first cousins but because first cousins are more likely to have common genes, some of which may be

deleterious. If no undesirable genes are present, first cousins can and sometimes do produce normal, or even superior, offspring. As we pointed out, it is the element of risk attached to consanguinity that makes it prohibitive. This element of risk is based on comparisons between expected common genes among relatives and population genes expected in common as a result of random mating. Our expectations about the relation between the incidence of consanguinity and the incidence of a genetic disorder are directly related to an understanding of population genetics.

The basic principle of population genetics is the Hardy-Weinberg law. According to this law, there is a predictable frequency of heterozygotes and of homozygotes present in the population at any one time. These frequencies, expressed as proportions, will always be stable or constant—"in equilibrium"—when various factors causing instability are not present. Factors causing instability include mutation, drift, gene flow, and nonrandom mating that includes the special case, consanguinity.

Application of the Hardy-Weinberg law is relatively straightforward when the frequency of an expressed trait in the population is known. Gene frequencies may be stated as probabilities, so that p is the probability of a normal allele and $1 - p$ or q is the probability of an abnormal allele. The probabilities of the genotypes are determined by expanding the term $(p + q)^2$ so that three genotypes are given: p^2, which is the proportion of the homozygous normal genotype, $2pq$, the proportion of the heterozygous carrier, and q^2, the proportion of the homozygous recessive genotype.

We can consider the use of this equation in analyzing albinism. Let us assume that the incidence of albinism in the population is one case among 10,000 persons. In terms of the expanded equation, this means that the frequency of the homozygous recessive genotype (q^2) is 0.0001. The frequency of the recessive gene, q, is the square root of 0.0001 or 0.01. The frequency of the dominant gene, p, equals $1 - 0.01$ or 0.99. With these values we can estimate the proportion of carriers, $2pq$, by multiplying $2 \times 0.01 \times 0.99$, which yields a value of about 0.02. Hence, one out of about fifty persons carries the gene for albinism.

One might well ask why, with such a high incidence of carriers in the population, there are not more albinos. The answer can be stated in terms of our calculation of odds. With random mating, the chances that two carriers will marry are $1/50 \times 1/50$ (1/2,500), and the chances that two carriers will have an albino child are 1/4. The combined chances that two carriers will marry and have an albino child are $1/50 \times 1/50 \times 1/4$ or 1/10,000, which is the estimate of the incidence of albinism that we used to derive our carrier frequency.

The same type of analysis can be carried out for any genetic disorder for which the incidence is known. Consider the rare recessive disorder, Wilson's disease. This has an incidence of one affected person out of a million people. By the same calculations we used in analyzing albinism, one can obtain for $2pq$ a value of about 0.002. This means that there is about one person in 500 people who is a carrier

for this disease. Obviously, the chances that two carriers will marry are quite low. In fact, the chances are so low that when this genetic disorder appears we assume that some instability among the frequencies of the different genotypes has occurred. It is for this reason that one factor causing instability—consanguinity—is often commonly found in families producing children with rare genetic disorders.

Mutations occurring in the parent generation change the genotype frequencies in offspring. Estimates of rates of mutation resulting from ionizing radiation, chemicals, and other causes have been made for a number of traits. Some of these estimates will be given in those chapters pertaining to the specific disorders.

Assortative or nonrandom mating, apart from consanguinity, can account for some of the disturbances of the equilibrium of genotype frequencies. From a sociologist's point of view, the Hardy-Weinberg law would be a theoretical approximation at best, because mate selection is almost always nonrandom. Intelligence, education, social class, geography, propinquity, and religion are but a few of the factors that govern regularities in the pairing of the sexes. Assortative mating certainly should be related to the appearance of traits resulting from polygenic inheritance. Some of these traits will be discussed in Chapter 5.

Genetic drift, by which gene frequencies change in subpopulations, and gene flow, by which population movement alters the gene frequencies, are additional factors that change the stability of genotypic proportions. In the main, these factors are not so important as mutation and consanguinity in causing disturbances in genetic equilibrium—yet they do contribute to our examination of some genetic disorders. The high incidence of the Ellis–van Creveld syndrome within one group of Amish settlers in Pennsylvania, and not within other Amish groups, can be understood best within the context of genetic drift. The study of the different blood group systems in American Caucasians and in American and African Negroes would indicate that the gene flow of Caucasian genes into the American Negro subpopulation is of some consequence.

An understanding of the Hardy-Weinberg law is important to the physician involved in genetic counseling because it provides a population base line for analyzing his patient. In addition, his consideration of the factors that disturb the Hardy-Weinberg equilibrium should make him especially attuned to consider many causal aspects of the genetic disease presented.

Unfortunately, since most of the harmful genes carried in the population are undetectable, the physician's consideration of mutation, consanguinity, etc., comes after at least one offspring has been afflicted. In those cases in which the genetic disorder is not manifest in early life, many children may be born before a genetic problem is discovered. Perhaps some day we will have tests to determine who carries what deleterious genes. Genetic counseling then will come before marriage or before childbearing.

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Chapter 5

Genes and birth defects

It is likely that every child born has a "birth defect," in the sense that he possesses some mental or physical blemish. These defects, many of which have a genetic origin, may be observable at birth; in some cases, they appear later in life. To cite but a few examples: cleft palate will be apparent at birth; pyloric stenosis will be detectable only after about 4 to 6 weeks of age; freckles, often inherited as a dominant trait along with red hair, usually will not be seen until a child is past his sixth or seventh birthday; premature balding, a dominant disorder affecting about half the male population, occurs in the third to fourth decade of life; diabetes mellitus may not appear until the fourth or fifth decade.

One in ten families experiences the birth of a child with an immediately *serious* hereditary disease. Diseases such as cystic fibrosis, hemophilia, or phenylketonuria are the major concerns and chronic burdens of families, physicians, and society. These diseases will prompt the questions we are asked most often about prevention in future offspring and "cure" for the affected child.

The family physician is also likely to be questioned about "normal" traits in the family. Curiosity alone may make some parents ask about their child's inheritance of intelligence, artistic abilities, personality, hair color, height, or weight. Much of our information about these and other human characteristics is still difficult to interpret solely on the basis of heredity. We will discuss this information in Chapter 10. In this chapter, we will concern ourselves more with the relationship of heredity to abnormal traits and diseases. For such a discussion, we have to explain the function of genes and the nature of gene changes called *mutations*.

GENES

The human zygote (which no one has yet actually seen) represents the union of the ovum, only barely visible to the naked eye, and the microscopically visible sperm. The new individual gets approximately equal contributions of hereditary material from the mother and the father. This hereditary material has been passed down from previous generations and eventually will be similarly contributed to future generations. All the successive generations of cells and of individuals carry one thing in common: the genetic material, deoxyribonucleic acid or DNA.

The genes have been described as being lined up on the chromosomes like beads on a string. The genes may now be described as part of a very esoteric coding machine that uses a four-letter alphabet: *A*, for adenine, *C*, for cytosine, *G*, for guanine, and *T*, for thymine. The genes can be truly visualized only through their effects on individuals, by which we recognize one individual as differing from another. It is obvious that a gene is identifiable, and is able to be "seen" only if there is *another* gene (an allele) present in a different form. If everyone had blue eyes and blond hair, it would not be possible to demonstrate that either eye or hair color is a "hereditary" trait. We must have differences among people in order to identify the presence of different genes. For example, we recognize the existence of a liver enzyme called phenylalanine hydroxylase only because we are able to detect certain "different" individuals who have phenylketonuria, a disease in which the enzyme is deficient. This condition also provides us with evidence that a single gene somehow controls the production of a specific protein. In this case, the protein is an enzyme, which when absent or deficient, causes a metabolic disorder with serious consequences.

Each single DNA "bead" on the coiled string (the chromosome) makes up a locus; each locus, of course, is present in duplicate. One locus is contributed by the mother and one is contributed by the father. The now classical Watson-Crick model of the DNA molecule, the double helical structure that resembles a spiral staircase, explains two things. It demonstrates the feasibility of the DNA chains carrying so many thousands of "genetic message units." It also explains in part the amazingly precise manner by which the DNA duplicates or copies itself for transmission of the genetic message to the next cell or to the next generation.

Sometimes the precise coding machines make an error, and there is a break in the precise continuum of genetic information. In fact, this book is primarily concerned with the phenotypic expression in individuals of such errors in the copying and transmission of the DNA material. The errors are generally referred to as mutations. To illustrate this point, in the hemoglobins of some individuals there is a substitution of one amino acid (valine) for another (glutamic acid), one of the 137 amino acids that make up one of the polypeptide chains. This seemingly minute change in the hemoglobin molecule results in the "sickling" phenomenon that is associated with chronic anemia and pathologic manifestations in all the organs of the body. We are not yet certain, however, where in the DNA chain the coding error arises that causes such a potentially lethal rearrangement of the amino acid chain in the hemoglobin molecule. The mutation or genetic change reflects itself in a change in the phenotype of the individual.

We will deal here primarily with such mutations in the germ cells or gametes, although later, in Chapter 12, we will suggest the possible occurrence of genetic errors in *somatic cells* in the etiology of malignancy. If the mutation occurs in a gametic cell (ovum or sperm), the odds are that one half of that future individual's offspring will inherit the mutant gene, and one half will have the "normal" (allelic) gene. Just as the DNA material is copied faithfully through countless cell genera-

tions and through many generations of individuals, so will be the mutant segment of DNA (unless the error is lethal enough to kill the individual). We can estimate that a spontaneous genetic change occurs in one out of approximately 50,000 genes in each generation, in each gamete (and occurring at a particular gene locus about every 100,000 generations or once every two million years!).

Theoretically, at least, each new zygote, each new individual, has the potential genetic makeup altered by one mutation. In fact, it is estimated that each person carries about five *lethal* mutant genes. Fortunately, these are recessive genes. A little later in this chapter we will discuss some of the ways in which mutations can be induced by such agents as radiation. The "mutations" involving rearrangements of whole segments of chromosomal material, such as breakage, translocation, and reunion of damaged chromosomes, will be discussed in Chapter 7. The remainder of this chapter will be devoted to the effect on the human population of mutations or genetic alterations involving single "beads" or loci on the DNA chain.

DISORDERS OF DOMINANT INHERITANCE

If a mutation occurs in one of the germ cells of an individual, producing a *dominant* trait, it is apparent that the offspring of this individual will show the abnormality. Thus, of the disorders with "single-gene" inheritance in man, we can recognize about eight times as many dominantly inherited traits as those that have a recessive pattern. This, of course, is probably artifactual, since there is great difficulty in detecting many recessive conditions, let alone relating them to a specific genetic etiology.

The origin of dominant genetic abnormalities by fresh mutations is very obvious indeed. Unless the mutation confers infertility along with its other phenotypic effects, the transmission of the new mutation can easily be observed in a family study or pedigree. In these families, with one parent carrying the dominant mutation (and the other parent normal, which is almost always the case), the affected parent will transmit the abnormal gene, on the average, to one half of his children. One can readily advise the parents of a child with such conditions as polydactyly, brachydactyly, or aniridia (congenital absence of the iris, causing blindness) that there is a 50% chance for each subsequent offspring to have similar anomalies. The diagnosis in these and most of the other autosomal-dominant disorders can be made early in the child's life because the child usually demonstrates obvious physical anomalies.

Calculating the risks in dominant disorders may become a little more involved in some instances when the disease is not so easily recognizable, although the same general rules hold. We were asked by an adoption agency to report the risks of a newborn infant's developing Huntington's chorea. The pedigree of the child's family shows clearly that this degenerative disease of the nervous system is the result of a simple dominant gene effect (Fig. 5-1). But the first signs of Huntington's chorea—the tremors, choreoathetotic movements, clumsy gait, or speech impairment—usually do not appear until the affected person is in his thirties or

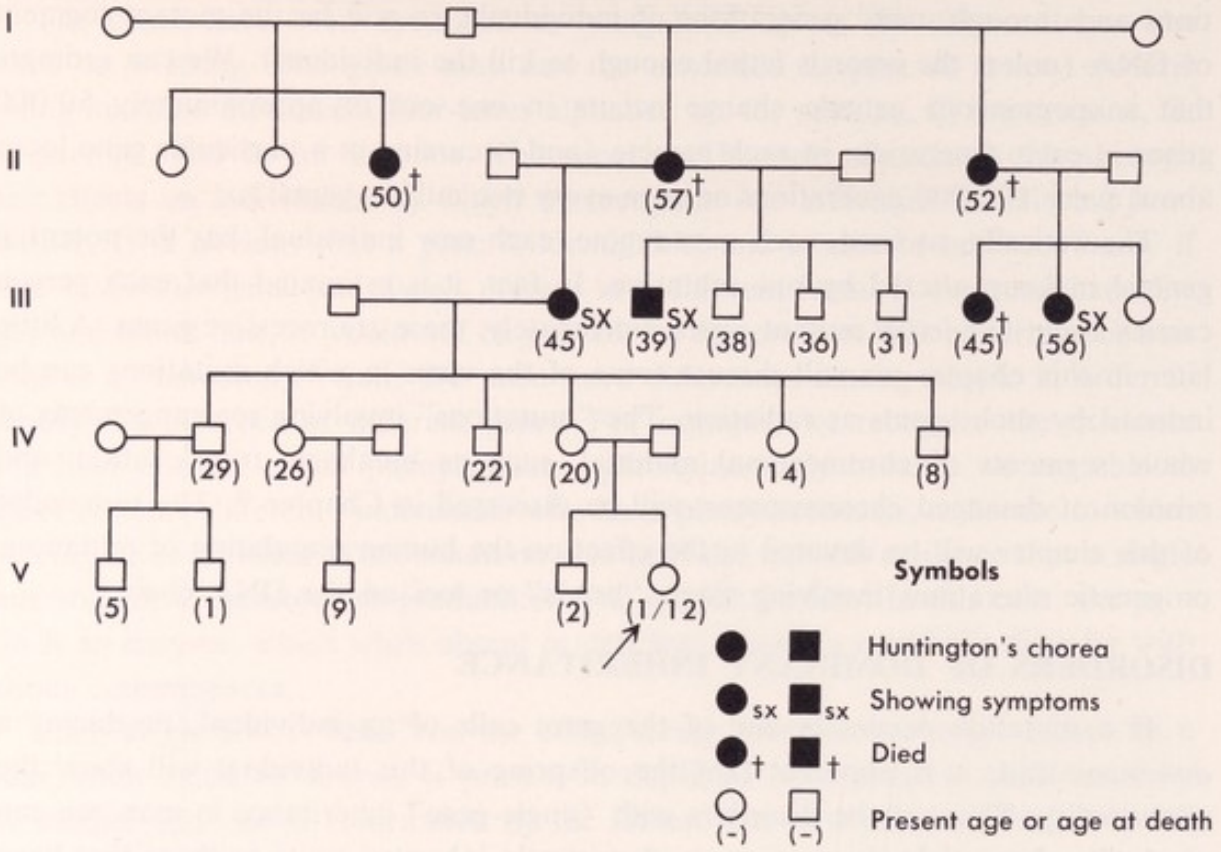

Fig. 5-1. Huntington's chorea in a family pedigree that demonstrates the dominant type of inheritance. Almost all the involved members of the family are presently in mental institutions or have died there.

early forties. Thus, there are no signs of the disease (even if the individual has inherited the mutant gene) until the person has had the opportunity to marry and bear several children. Each of these children has a 50% chance of receiving the gene from a parent if the parent manifests the disease. The dominant type of pedigree in this family shows that the risk of the mother having the disease, and ultimately manifesting it, is 50%. The probabilities that the newborn has the gene is thus ½ × ½ or ¼, or 25%. Certainly, the adoption agency (and the prospective parents) should be made well aware of the significance and meaning of these odds.

Since there are no tests available to detect those individuals in the family destined to develop Huntington's chorea, there is frequently an unwillingness on the part of family members to accept advice against having children. One can only present the facts to the younger family members and hope that they will forego procreation and further dissemination of this disease.

Another complication arising in the counseling of families with autosomal-dominant disorders is that of *penetrance*. The unaffected parents of a newborn child with achondroplasia can be assured that they themselves are not *heterozygous* for the gene, and that recurrence in future offspring would be unlikely. (About 1 in 12,000 is the approximate incidence in the general population of

births of children with this malformation.) Achondroplasia, like so many of the dominant disorders, is fully *penetrant,* in that the manifestation of the disease—a defect in ossification, leading to dwarfism—is always evident (Fig. 7-15). On the other hand, osteogenesis imperfecta ("brittle bones disease"), another disorder with a dominant mode of inheritance, may vary in its clinical manifestations, from individual to individual within a family, and from family to family. One individual may have the full-blown syndrome: bone fragility with a liability to fractures, blue sclerae, ophthalmologic defects, and otosclerosis (deafness). Other persons may be *"formes frustes,"* demonstrating only one or several of the specific abnormalities. A careful examination (and a thorough family history) will be necessary to decide whether the disorder has already existed in the family for some time or a "fresh" mutation has occurred.

Penetrance or "expression" of genes may therefore be defined in terms of the visible effect on the phenotype of the individual. The physician must be familiar with the diseases that apparently "skip" generations, but in reality have been expressed only in mild and unnoticeable ways. To provide an example, we recently saw an infant with hereditary spherocytosis. Seemingly, this disease, which we detected by the characteristic spherocytic-shaped cells on the peripheral blood smear, had appeared "suddenly" in the family. A careful history, however, elicited the fact that a maternal grandmother had recently had a cholecystectomy because of gallstones. Examination of the red cell morphology of the entire family revealed that the spherocytosis was indeed present in the mother, one other sibling, and the maternal grandmother. Again, in certain dominant disease states, identification of an affected individual demands careful scrutiny of all members of the family, despite the apparent absence of clinical signs.

RECESSIVELY INHERITED DISORDERS

Generally, the pedigree of a family will clearly demonstrate dominant inheritance, except for the apparent skipping of generations. But it is often difficult to identify a recessive form of inheritance of a disorder from an examination of a single family tree. The mutant gene that causes a recessive condition, such as cystic fibrosis, phenylketonuria, and the vast majority of the "inborn errors," is masked in the heterozygote by the normal allelic gene. Thus we have to look for certain clues pointing to recessive inheritance in the pedigree. These clues include consanguinity of the parents who are clinically normal, the 3:1 ratio of normal to affected children in those families in which the parents are normal, and usually all normal offspring from the marriage of a normal and an affected person.

The presence of hereditary factors influencing specific traits may be disclosed by observing population groups, as well as through twin or family studies. Swedish and Japanese studies of inbred children (by consanguineous marriages) have shown that intelligence quotients are lower, on the average, than those of control children. The lower intelligence scores in such inbred children may be attributed

to changes in the action of genes governing intelligence. In effect, the genes have been made homozygous by consanguinity. Similarly, consanguinity among the more intellectually endowed families seems to lead to higher intelligence quotients and superior intellectual development.

Even genes that are "recessive" in regard to the actual cause of disease may often be detected by measurement of an enzyme or of a protein whose production they regulate. At the beginning of this chapter we mentioned sickle cell anemia. The heterozygote "carrier" of the sickle gene shows no clinical manifestations of the disease; however, electrophoretic techniques can detect the presence of about 40% of the abnormal sickle hemoglobin in these so-called "S-A" individuals. Similarly, the heterozygote for phenylketonuria, galactosemia, and some of the other recessive metabolic disorders can be identified by appropriate biochemical studies. Many of these disorders, which have been related to recessive gene inheritance, are discussed in Chapter 11.

DISORDERS OF "MULTIFACTORIAL" INHERITANCE

Many of the disorders that present common counseling problems for the practicing physician offer no "simple" genetic pattern of inheritance. In fact, some congenital defects may be related to environmental factors alone or to combinations of genetic and environmental factors. In this section, we will discuss several of the more common congenital defects and summarize the "risks" of other common malformations in Table 5-1. Instead of relying on Mendelian rules to calculate probabilities of recurrence in a family, the counselor must use empiric risk tables. Empiric risks are determined by studying the incidence of recurrence of certain defects in the relatives (especially siblings) of affected individuals. If the frequency of affected siblings does prove to be significantly higher than in unrelated individuals, a familial tendency is demonstrated—but this tendency also can be due to certain familial environmental factors as well as to genetic factors. For such abnormalities as cleft palate and meningomyelocele, the genetic mechanisms, as well as the influence of environmental factors, remain relatively unknown. Counseling obviously is a more difficult task in such cases.

One of the more frequent problems in genetic counseling is the situation in which a couple has had one or two children with anencephaly, spina bifida with meningomyelocele, or hydrocephalus. These central nervous system anomalies are good examples of the defects apparently caused by an interaction of genetic (and *polygenetic*) factors and intrauterine environmental factors. Table 5-1 indicates that the risk of recurrence in a family after one affected child has been born is about 5%. This risk is about twenty-five times greater for these families than for those families representing the general population. These are the "genetic high-risk families." Since one or another of the nervous system malformations may recur in a family, there is some evidence that this group of defects represents a continuum of developmental errors in the embryonic neural tube. Usually malformations of the same type are found to recur in families. The risk of recurrence in a

Table 5-1. Empiric risks for specific birth defects

Birth defect	*Incidence in United States population (%)*	*Sex ratio M.:F.*	*Risk of recurrence after one affected child is born*	*Risk of affected parent having an affected child*
Pyloric stenosis	0.3	5:1	1 in 16 (1 out of 50 if first child was male, 1 out of 10 if female)	1 in 16
Congenital dislocation of hip	0.075	1:10	1 in 20	1 in 20
Clubfoot	0.085	2:1	1 in 20	1 in 15
Cleft palate	0.04 (0.02 in Negroes)	2:3		
Cleft lip (with or without cleft palate)	0.1	2:1	1 in 15 to 25	1 in 50
Spina bifida (associated with meningomyelocele)	0.3	1:1	1 in 20 (1 in 10 after second affected child is born)	
Hydrocephalus	0.2	1:1		
Anencephaly	0.2	1:3		
Hirschsprung's disease (intestinal agangliosis)	0.02	7:1	1 in 25 to 33	1 in 20
Microcephaly	0.1	1:1	1 in 9 (1 in 4 after second affected child is born); very frequently is autosomal-recessive	

family with one affected child is thus 1 in 20, which is about twenty-five times greater than the risk in the general population. This risk figure doubles to 1 in 10 after the birth of a second child with a similar malformation.

We noted for the recessive disorders, such as cystic fibrosis or albinism, that the risks of recurrence never change. The recurrence risk in the family with an affected child (homozygous for the mutant gene) remains 1 in 4, whether the parents have one, two, three, or more affected children. On the other hand, changing risks—up to 10% for recurrence of spina bifida after two children have been born—along with the different rates for the disease among various ethnic and socioeconomic groups (and in different geographic regions of the United States) indicate that environmental influences of some sort are important.

In addition to the increased chances of recurrence of central nervous system malformations, high-risk families also have a threefold increased risk for other types of birth defects, and an increased incidence of abortions.

Table 5-1 likewise illustrates the use of empiric risk figures for counseling families with members affected by other congenital defects. Cleft palate and cleft lip (with and without the presence of cleft palate) seem to have both genetic and nongenetic factors operative. The risk of recurrence in a family that has a child born with cleft palate is on the order of one-hundredfold. The risk to the child of a parent who himself had a cleft palate anomaly is 7%. This risk is much higher than the risk for the population as a whole. The etiology of isolated cleft palate apparently is genetically distinct from cleft lip (harelip) with or without an associated cleft palate. The incidence of cleft lip is high among relatives of individuals with cleft lip, but the occurrence of cleft palate in this same group is unusual. Similarly, relatives of an individual with cleft palate have a higher incidence of the same defect, but they are less likely to have a cleft lip.

As we will see for other disorders with "multifactorial" inheritance, nongenetic factors play an influential role in producing cleft lip and cleft palate. This is reflected in the fact that the majority of monozygous twins do not show concordance for cleft palate or cleft lip. Experimental work on animals even indicates that clefts can be induced by a variety of teratogenic agents or by dietary deficiencies. These studies suggest that similar etiologic factors might produce these conditions in humans.

In summary, cleft lip and cleft palate, like central nervous system defects, present us with problems of etiology. These disorders may be strongly inheritable in some families because of the action of a genetic factor that acts as a dominant. In other families, they may be less inheritable because several genes have to interact to produce the anomalies. Finally, the defects may be sporadic in occurrence because they result from environmental factors that can mimic the deformities induced genetically.

The complexity of counseling families concerning the recurrence of defects might best be illustrated by the following case that came to our attention. The first child of apparently normal parents had cystic fibrosis and died early in infancy as a result of an intestinal obstruction. Their second child had spina bifida with meningomyelocele and died at 1 year of age after having developed hydrocephalus following a surgical repair procedure. The parents wanted to know the chances that their next child would be normal. Our estimation of the risks was a sum of the risk of cystic fibrosis (25%) and spina bifida (5%), so that we could offer this couple a chance of approximately 70% for having a normal baby.

DISORDERS THAT "RUN IN THE FAMILY"

There is another group of disorders that exhibits an irregular pattern of inheritance. These conditions tend to "run in families," but the evidence is not unequivocable that genetic factors alone are the etiologic agents. These disorders, also

called "constitutional" disorders, include asthma, duodenal and gastric ulcers, pernicious anemia, and diabetes mellitus. Gout, coronary artery disease, hypertension, the psychoses, and epilepsy also show unique familial grouping, as we will reiterate in Chapter 10.

The prevalence of these conditions makes it highly likely that they will be encountered by physicians more than the single-gene (monogenic) conditions. Unfortunately, genetic questions are seldom entertained by physicians about these conditions because of their elusiveness in terms of familial recurrence, age of onset, and lack of "carrier" identity. Genetic advice often comes only after arduous examination of pedigrees and family histories. Genetic risks are, at best, based on empiric risk tables, and, as we discussed in Chapter 4, genetic counseling may be complicated by that fact alone.

Investigation of the genetic role in many of these diseases is at a relatively early stage. For example, although diabetes mellitus is one of the most common disorders in our society (affecting 1 in 100 persons at the age of 25 to 45 and 4 in 100 by the age of 65), we are not certain about the basic defect involved. It is speculative whether the cause of diabetes is due to abnormal insulin, a lack of response to insulin, the presence of an insulin antagonist, or an error in carbohydrate metabolism. The role of genetic factors related to these speculations is equally speculative. Family clustering of diabetes mellitus has long been noted, and, in many of these families, the disease acts like an autosomal-recessive abnormality. The risks for diabetic mothers are that, on the average, one half of their children will ultimately develop the disease. Diabetes among identical twins shows a highly shared incidence rate, and the offspring of conjugal diabetics (both parents affected) also have a high incidence rate. Therefore, diabetes would seem to be inherited; yet some of the twins and some of the children of diabetic parents do not develop the disease. In any event, it is important to detect the "prediabetics." This may be done by using the glucose tolerance test or some similar test.

ENVIRONMENTAL FACTORS (TERATOGENS) AND CONGENITAL DEFECTS

We have outlined the *purely* genetic diseases and those malformations that are due to a combination of hereditary and environmental factors. There is a third group of malformations that are caused by certain teratogens (from the Greek word meaning monster). Frequently, these "monster-like" anomalies mimic those defects that are genetic in origin, and thus are phenocopies of the hereditary disorders. The similarity of some of the genetic and nongenetic anomalies indicates that "insults" occurring at the same stage of embryonic development damage the same organs. In addition, because the changes in organs are related to the age of the fetus, the time at which the fetus is exposed to the teratogen is important. It is for this reason that we try to elicit a thorough history of a woman's pregnancy when children with birth defects are seen in our clinic.

One example of such a malformation is microcephaly, which occurs in approxi-

mately one in 1,000 live births. Many of these microcephalic individuals, who are invariably mentally retarded, are homozygous for an autosomal-recessive mutant gene. A good many such cases, however, are probably phenocopies caused by such known teratogenic factors as x-ray exposure, cytomegalic inclusion virus infection during pergnancy, or some other yet-undocumented agents. In the empiric risk table, the possibility of recurrence of the microcephaly in a second child is not 25%, but about 12%. After a second microcephalic child is born, one must bow to the inevitable and make the diagnosis of a recessive condition. From then on, the risk is the expected 25% or one in four.

Radiation, genes, and chromosomes

Since the first large-scale clinical trial of the effects of exposure to ionizing radiations at Hiroshima and Nagasaki, over twenty years ago, there has been a special interest in showing the relation between radiation and disease. Although we tend to worry most about radioactive fallout and the amount of radioactive strontium in the milk our children drink, the gonadal exposures from radiologic diagnostic procedures also offer a great deal of potential risk to individuals. In fact, there are two kinds of risks, the somatic and the genetic. "Somatic" simply indicates that the risk is to the individual himself, and "genetic" indicates that the risk is to the individual's offspring and future generations.

It has been firmly established by laboratory experimentation that radiations cause mutations. In addition to man-made radiations, natural radioactive agents in the environment add to the total dosage effect. From our knowledge of the *half-life* of these radioactive materials, we recognize that while some of the materials are new, some have been present for several billion years. The materials, present in the soil, plants, and the atmosphere, irradiate us throughout our normal life and likely cause some of the "spontaneous" mutations such as those that sporadically produce achondroplasia or hemophilia. While an estimate of the genetic damage to humans from omnipresent natural radiation is speculative, we can examine with more certainty the effects of radioactive fallout and medical radiation.

Milk is the most important source of radioactive contamination, because of its place in a natural food chain. The route of radioactive fallout from the atmosphere to milk follows a course by which it enters the ground, is concentrated in grass or grains, and is further concentrated in the milk of cows eating the grass. Children, the greatest human consumer of milk and milk products, face the greatest exposure to such radioactive materials as iodine 131, strontium 90, and cesium 137. In the main, these materials accumulate in the body according to their natural selective usefulness. Radioactive iodine apparently accumulates in the thyroid, and radioactive strontium accumulates in the bones or similar tissues. A measure of the accumulation of radiation in children has taken account of this selectivity. For example, the baby-tooth survey has proved to be an effective way to measure the accumulation of strontium 90 in the bones of children. Examination of the

deciduous teeth of children during the years since nations began testing atomic weapons has indicated that there is a correlative rise and fall between the amount of strontium 90 in teeth and the amount of atmospheric contamination. Since the half-life of strontium 90 is 28 years, it is obvious that the effects of fallout are not temporary.

The degree to which radioactive fallout has already altered the genetic constitution of the population is unknown. We are not even sure what constitutes a safe level of radiation, or whether there is a "safe" level of all individuals. We are sure, from surveys on children and postmortem examinations, that radioactive materials are already present in the bones and other tissues of most human beings.

There is good evidence that pelvic irradiation (primarily from therapeutic

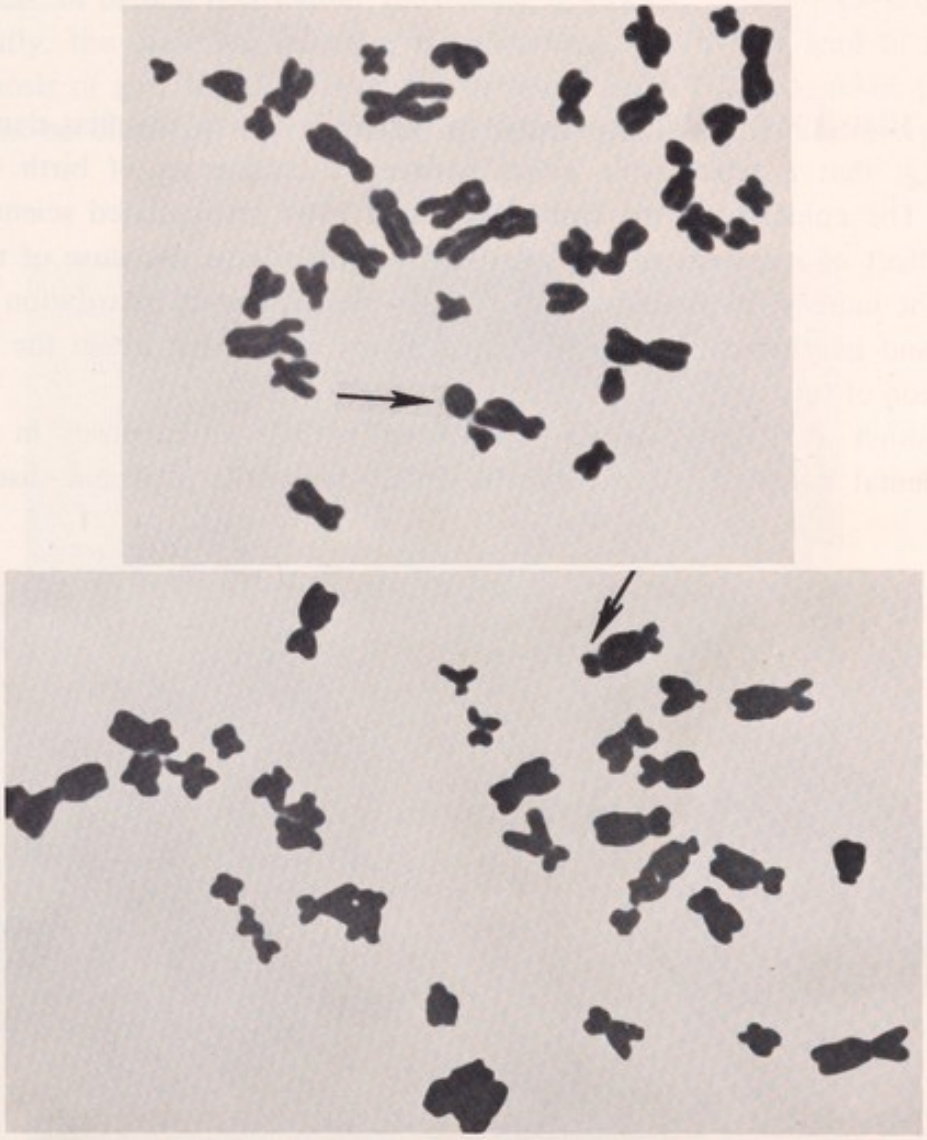

Fig. 5-2. Chromosome aberrations in leukocyte cultures of an individual exposed to irradiation. The ring chromosome on the left and the dicentric chromosome on the right are indicated by arrows. Both of these anomalous chromosomes are caused by chromosomal breakage and reunion. (From Reisman, L., et al.: Radiology **89**:75, 1967.)

dosages) during pregnancy can cause microcephaly. A significant number of the Japanese children who were in utero in mothers exposed to the atomic bomb blast also developed microcephaly. The number of cases of microcephaly was directly related to the distance of the pregnant woman from the hypocenter of the atomic blast. The majority of the damaged infants were born to mothers exposed within the 7-week to 15-week period of pregnancy, determined by the last menstruation. The risk of developing leukemia and other malignancies also seems to be significantly increased after radiation exposure in childhood (or even in utero). We will present some information on the possible carcinogenic effect of radiation in Chapter 12. Our own investigations, as well as studies by others, seem to indicate that the usual diagnostic doses of radiation do not cause chromosome damage, although therapeutic doses of radiation and accidental exposures to large amounts of radiation have been reported as being related to persistent chromosome abnormalities (Fig. 5-2).

Viruses

The 1940-1941 rubella epidemic in Australia led to the first demonstration, by Gregg, that a relationship exists between a unique set of birth defects and rubella. The epidemic in the United States in 1964 restimulated scientific interest in the effect of maternal rubella on the developing fetus. Because of the last epidemic, the increase in the number of patients seen at mental retardation centers and speech and hearing clinics in the United States will be felt about the time of the publication of this book.

Although a large group of viruses (up to 300 millimicrons in size) cross the placental barrier, only the rubella and cytomegalic inclusion disease viruses

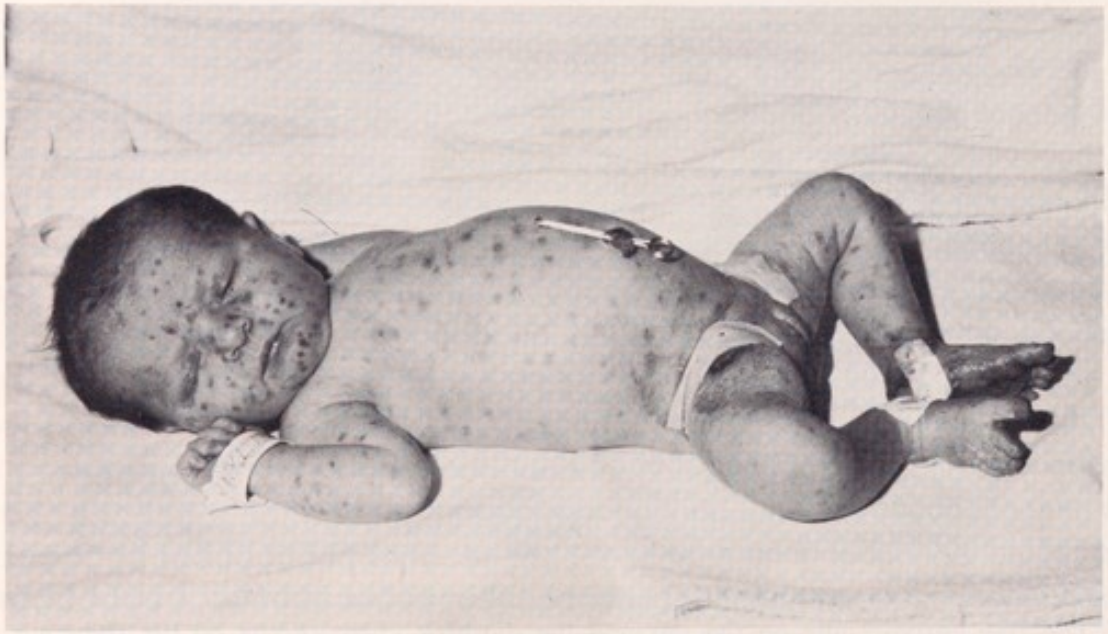

Fig. 5-3. Newborn with "blueberry muffin" hemorrhagic rash caused by rubella infection in utero.

have been incriminated as teratogenic agents (Fig. 5-3). The rubella virus can infect the fetus and persist in the newborn's tissues for many months. Excretion of the virus in the urine has been shown to occur as long as 18 months after birth of the infant with the rubella syndrome. Although the original retrospective reports indicated an incidence of malformations in approximately 90% of the children whose mothers had rubella in the first trimester of pregnancy, the incidence estimated now is less than that figure. The percentage of children with defects is now in the range of 10% to 30%. Even this lower incidence is striking if we compare it with the usual 3% incidence of anomalies in the general population of newborns. Also, we should remember that about 10% to 15% of rubella-affected pregnancies end in spontaneous abortions. Whether or not one considers high the incidence of malformations or spontaneous abortions, to the families who have children with such conditions as congenital heart disease, cataracts, deafness, or mental retardation, the disease is serious.

Frequently, the maternal infection is *subclinical,* which may lead to an erroneous diagnosis of an allergic reaction or "nervous" rash. This diagnostic problem, however, can be offset by new serologic techniques that, in the laboratory, estab-

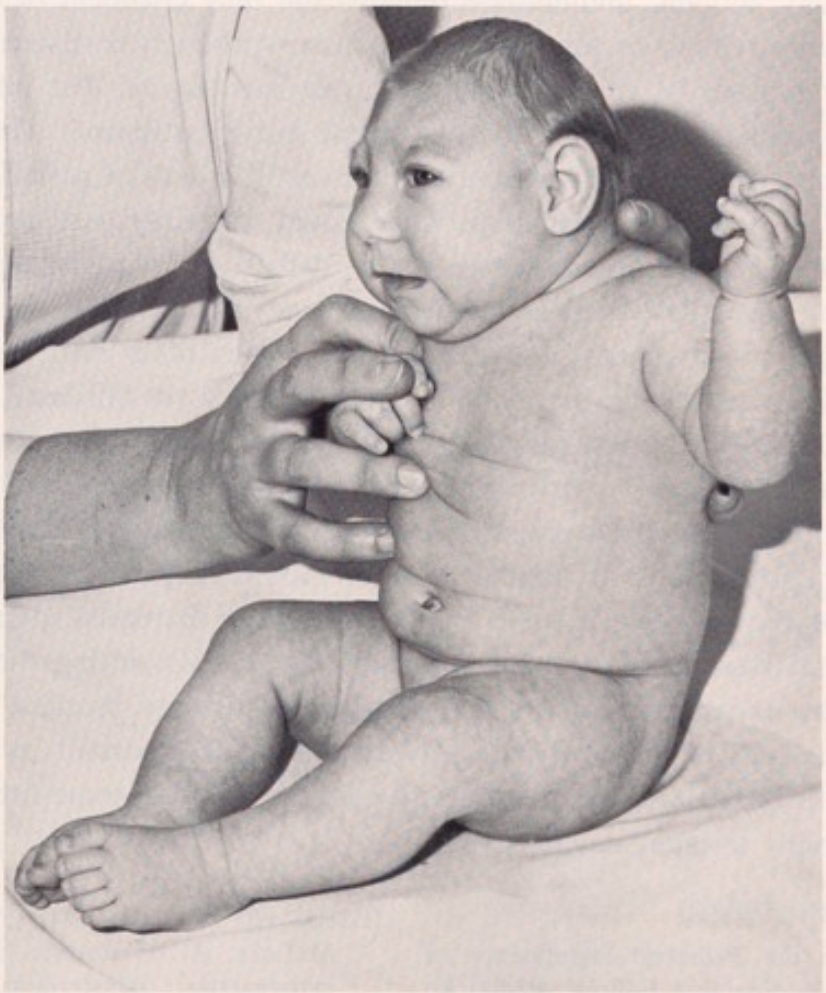

Fig. 5-4. Three-month-old child with microcephaly.

lish the presence of the disease. The development of active immunization against rubella will also make the disease less threatening as a diagnostic (and medical) problem.

Cytomegalic virus infection in the mother is almost always subclinical. Infants probably acquire the virus during the early months of pregnancy, since microcephaly and other brain anomalies found in infants with congenital cytomegalovirus infection (CMV) are suggestive of teratogenic effects during the third or fourth fetal months. At birth these infants almost always show hepatosplenomegaly and jaundice. A correct diagnosis depends upon the detection of the typical inclusion bodies in epithelial cells and urine sediment, intracranial calcifications, and the frequent presence of chorioretinitis.

Drugs

A large-scale experiment in the testing of durgs for teratogenic effects was the use of thalidomide in pregnant women in the early 1960's. Many thousands of babies developed the "thalidomide type" of malformations—phocomelia, absent or hypoplastic ears, and many other associated congenital anomalies—from use of this drug during an apparently sensitive period, thiry-four to fifty days after the last menstrual period.

Interestingly enough, thalidomide remains the only chemical or drug that has been specifically related to teratogenesis in man. Although cortisone induces cleft palate in the mouse, its effect in man is purely speculative. The infant shown in Fig. 5-4 was seen in our clinic for placement in an institution. The mother had been given intravenous hydrocortisone in the second month of gestation because of an "allergic" reaction to penicillin. One could certainly not prove with this single case that steroids are the cause of the defect. One could suggest, however, that all females be questioned about their last menstrual period (or questioned if they know they are pregnant) before cortisone or any other drug is prescribed.

The LSD (lysergic-acid diethylamide) story is not yet finished. LSD (as well as many radiomimetic drugs, radiation, and viruses) causes chromosomal damage to leukocytes in vivo and in vitro. There has been, however, no established teratogenetic effect documented for pregnant women, even though there have been several reports of malformations in infants born to mothers who took the drug during pregnancy. Moreover, there is some scanty evidence of increased spontaneous abortions and fetal wastage in women who had taken LSD during their pregnancy. LSD taken by expectant mothers has also been shown to produce chromosomal damage in the cells of the newborn. The last finding is important, as we will relate in Chapter 12, because of the relationship between "chromosome-breaking ability" and susceptibility to malignancies.

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Chapter 6

Counseling in Down's syndrome

Almost 100 years after the English physician John Langdon Down first characterized the mongoloid as a mysterious retrogression to the Mongolian race, Lejeune and his co-workers in 1959 published their observations of an extra small body, a forty-seventh chromosome, in fibroblast cultures obtained from nine mongoloid children. It was suddenly apparent that the cause of Down's syndrome was a reduplication of one of the chromosomes of the twenty-first pair (trisomy 21), the extra genetic material somehow leading to the generalized dysplastic development of organs and tissues that is so characteristic of this disease.

Each year, the parents of over 7,000 new infants with Down's syndrome in the United States alone are faced with the many problems associated with raising these mentally and physically damaged children. The abnormality occurs about once in every 600 to 700 births and is found among persons in all social and economic strata. Since it is the family doctors who are most frequently consulted about the problems raised by the birth of a mongoloid child, they should be especially familiar with current concepts of the etiology of the disease, some basic facts of human cytogenetics, and guidelines for sympathetic, but informed and intelligent, family counseling.

The need for genetic counseling has been recognized; unfortunately, however, it has often been provided by individuals competent in their own fields but ignorant in the areas of both genetics and mental retardation. The parents of children with Down's syndrome want to know the cause of the abnormality and their chances of having a similarly affected child in the future. These parents also want to know how tall their child will be; they want to know how long his life-span will be; and they want to know what the child's level of intellectual achievement will be. The purpose of this chapter is to discuss current knowledge of the cytogenetics of Down's syndrome, to present ideas concerning the developmental abnormalities involved in this disease, and to explain the use of these facts as a foundation for effective family counseling.

TERMINOLOGY: "DOWN'S SYNDROME" OR "MONGOLISM" OR "MONGOLOID"?

The racist overtones of the words "mongolism" or "mongoloid" certainly disturb many individuals. Down's interpretation of the mongoloid peculiarities as representing a reversion to Mongolian stock was based primarily on superficial facial characteristics. He wrote in 1866, in "Observations on an ethnic classification of idiots," that a mongoloid is a

> representative of the great Mongolian race: When placed side by side it is difficult to believe that the specimens are not children of the same parents. The hair is not black, as in the real mongol, but of a brownish color, straight and scanty. The face is flat and broad and destitute of prominence. The cheeks are roundish and extended laterally. The eyes are obliquely placed and the internal canthi more than normal distance from one another. The palpebral fissure is very narrow. The forehead is wrinkled transversely from the constant assistance which the levatores palpebrarum derive from the occipito-frontalis muscle in the opening of the eyes. The lips are large and thick with transverse fissures. The tongue is long, thick, and much roughened. The nose is small. The skin has a slight dirty, yellowish tinge, and is deficient in elasticity, giving the appearance of being too large for the body. . . . there can be no doubt that these ethnic features are the result of degeneration.*

However, before we can discard "mongolism" and "mongol," other acceptable terminology must be decided upon. "Down's syndrome" or "anomaly" is a reasonable alternative but remains an unfamiliar term to many parents and even quite a few physicians. It is obvious that since such anachronisms as "cretinism" (derived from the word "Christian") and "aorta" (air tube) are firmly entrenched in our medical vocabulary, the reformers may find it very difficult to eliminate the term "mongolism" from the scientific literature, let alone from general usage.

ETIOLOGY OF DOWN'S SYNDROME

Historical perspectives

There has never been a scarcity of ideas concerning the etiology of Down's syndrome. An early authority on this condition described mongoloids as "unfinished children," intimating that some depressing influence on the mother's powers caused incomplete development of the infant in utero. Down, himself, considered parental tuberculosis to be the primary causal factor, but alcoholism, syphilis, epilepsy, mental disease, and thyroid disease have also been blamed by various investigators. A narrow amniotic sac that prevented full development of the fetus has been cited in explaining the anomaly, as have been accidents to the mother during pregnancy, poor maternal nutrition, and intrauterine infections.

However, even the originator of the term "unfinished children," Shuttleworth, in 1866, noted that ". . . nearly one-half of these children are the last born of a long family," though he was unable to decide whether the anomaly was due to the advanced age of the mother or the excessive maternal parity. Other workers also observed that the births of mongols were associated with pregnancies at the end of large sibships. This finding led to increased speculation that the cause

*From Down, J. L.: London Hospital Clinical Lecture Reports **3:259,** 1866.

of mongolism was related to aging of the ovum, or at least to some injury to the maternal germ cells, which could be attributed to the mother's age and birth order of the child.

Maternal age factor

In 1933, Penrose demonstrated conclusively that there is indeed a relationship between Down's syndrome and maternal age, regardless of the number of children born previously. Age of the father, just as conclusively, was shown statistically to have no effect on the incidence of mongolism. There is also no evidence that either too short or too long an interval between pregnancies is of direct significance in the etiology of Down's syndrome. If the long interval between pregnancies has been an involuntary one, however—in that there has been difficulty in becoming pregnant, or there has been a series of abortions—some predisposing factors may be present. These predisposing factors will be discussed later when we discuss familial mongolism.

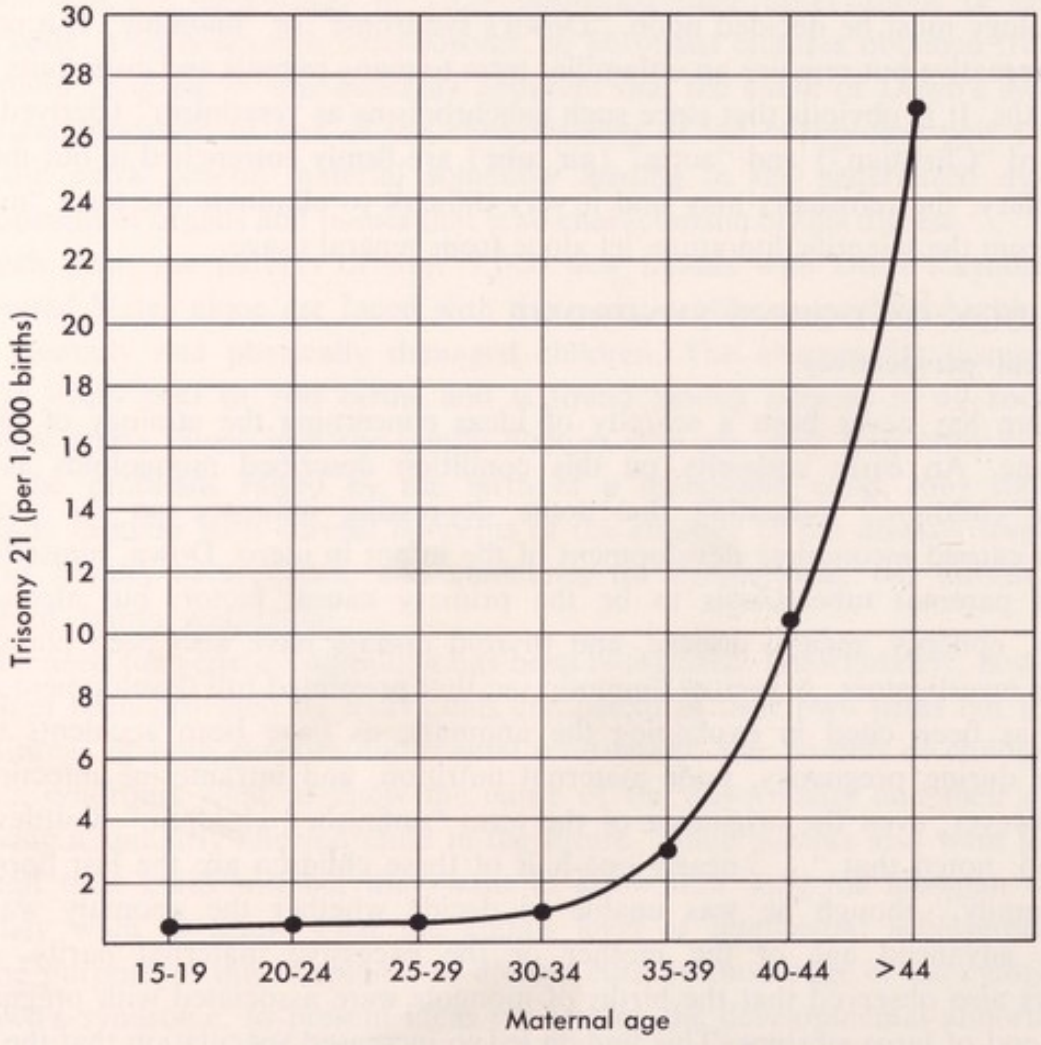

Fig. 6-1. Curve illustrating the accelerating rate of increase of Down's syndrome in the offspring of mothers over the age of 30.

Fig. 6-1 demonstrates the tremendous increase in frequency of mongoloid births to mothers in the older age groups. Although the incidence of Down's syndrome is approximately one in 1,000 to 2,000 births among mothers who are 19 to 29 years of age, there is a sharp rise in the curve after the age of 30. In the maternal age group between 35 and 39, the incidence rises to about three mongoloid births per 1,000. In the group from 40 to 44 it rises to about eleven births per 1,000, and in the group over 45 years of age, the incidence is close to one in 30 to 50 births.

Origin of the extra chromosome

The chromosomal anomaly associated with Down's syndrome is a duplication of one of the chromosomes of group 21-22, usually considered to be number 21 (Fig. 6-2). In simple terms, there is an extra chromosome 21. How the extra chromosome arises is obviously a vital factor. Therefore, it is worthwhile to examine briefly some of the basic facts well known in human genetics.

All the diploid (46 chromosomes) somatic cells in the adult are derived from the zygote, the fertilized egg, which is produced by the union of two haploid (23 chromosomes) gametes, the sperm in the male and the egg in the female. The mechanism for this reduction in chromosome number is called *meiosis,* and the proper separation of the two chromosomes comprising each chromosome pair during the second stage of meiosis is essential for maintenance of the chromosome number. Separation of the pair of chromosomes is described as *disjunction.* If the disjunction proceeds correctly, the gametes (spermatozoon and ovum) will be found

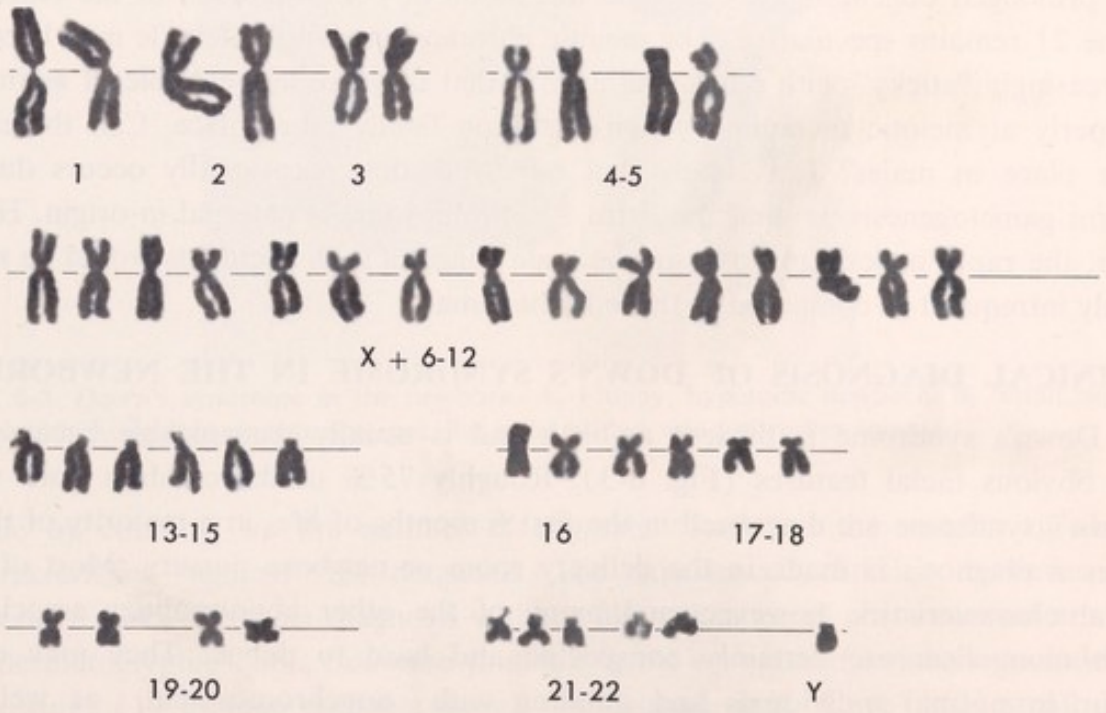

Fig. 6-2. Karyotype of the "classic" trisomy of chromosome 21.

each carrying the haploid number of chromosomes with the genetic material divided equally. During meiosis, the chromosomes line up in pairs; ultimately one chromosome from each pair goes to the daughter cell, ensuring an equal division of the chromosomal material. Thus, normally, the number 21 chromosome lines up opposite the other number 21, and each of these autosomes goes to one of the daughter cells. When normal separation of the chromosomes fails to occur and both chromosomes migrate together to the same daughter cell, the resulting gamete will have an extra chromosome. The phenomenon of improper separation of chromosomes (or of improper association in pairs of these chromosomes) during meiosis is called *nondisjunction;* it now appears likely that this accident is the reason for the extra chromosome and the resulting genetic excess of Down's syndrome. Although it is apparent that zygotes with absence of a chromosome will be produced, these cells are less viable than trisomic cells and will probably almost always perish. (However, at least one individual with apparent monosomy of a 21-22 group chromosome has been described, so that autosomal monosomy is apparently not invariably lethal.)

How advancing maternal age is in turn related to the accident of nondisjunction may now be reconstructed. It has been demonstrated in man (and in other mammals) that the female's germ cells have already begun meiosis and maturation while she is still in utero. The several hundred or so ova then remain dormant (at the dictyotene stage) until ovulation occurs at the onset of the menarche. Then at regular monthly intervals single ova resume the meiotic process and are released. Thus, while new spermatocytes are constantly being formed in the male—there being a rapid and continuous production of sperm from puberty on—potential ova may remain in meiosis in the ovary for many years. The mechanism by which the prolonged oogenesis increases the likelihood of nondisjunction of the chromosome 21 remains speculative. The meiotic chromosomes of the female may become increasingly "sticky" with advancing age, in that they are less capable of assorting properly at meiotic metaphase when ovulation finally takes place. Can the error take place in males? It is likely that nondisjunction occasionally occurs during sperm gametogenesis, so that the extra 21 chromosome is paternal in origin. However, the rapid meiotic turnover in the male suggests such accidents would be relatively infrequent as compared to those in the female.

CLINICAL DIAGNOSIS OF DOWN'S SYNDROME IN THE NEWBORN

Down's syndrome is present at birth and is usually recognizable because of the obvious facial features (Fig. 6-3). Roughly 75% of the children born with Down's syndrome are diagnosed in the first 6 months of life; in a majority of these cases a diagnosis is made in the delivery room or newborn nursery. Most of the facial characteristics, however, and many of the other abnormalities associated with mongolism are certainly nonspecific and hard to define. They may even occur in normal individuals and children with nonchromosomal, as well as chromosomal, conditions. Thus, very often the diagnosis of Down's syndrome is

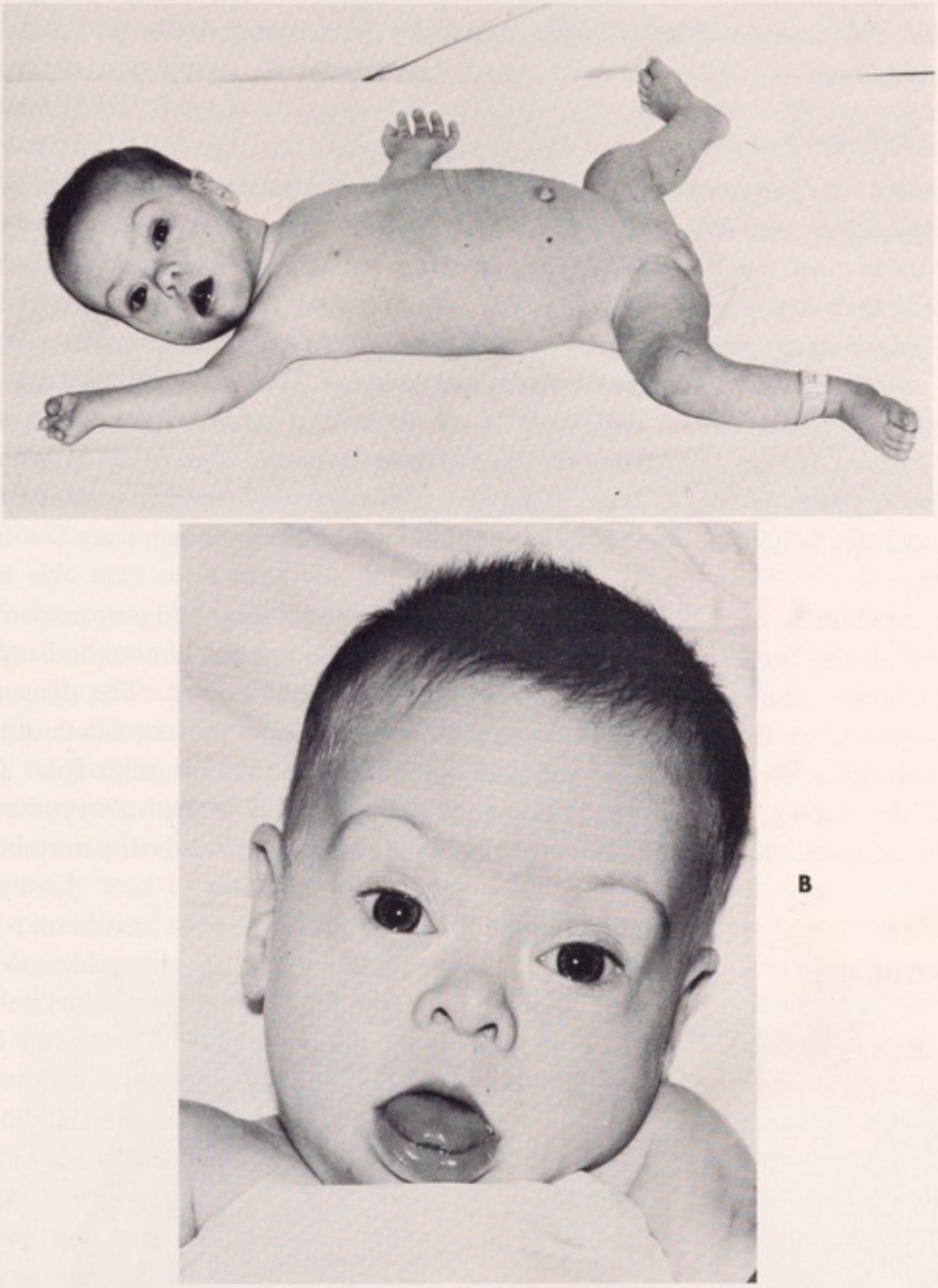

Fig. 6-3. Down's syndrome in the newborn. **A,** Floppy, hypotonic newborn. **B,** Small, square head with mongoloid slant to the eyes, flat nasal bridge, and protruding tongue.

made by counting up the number of stigmata "for" and the number of absent characteristics "against" the diagnosis. The experienced clinician, however, can generally make a correct diagnosis without the assistance of chromosomal analysis or dermatoglyphic data. *Common findings in the mongoloid newborn* include the following: (1) oblique palpable fissure (mongoloid slant of eye), (2) small, low-set, dysplastic ears, (3) brachycephaly, (4) protruding tongue, (5) simian line

(unilateral or bilateral), (6) clinodactyly (fifth finger), (7) hyperflexibility, (8) hypotonia, (9) absence of Moro reflex, and (10) decreased pelvic angle on radiographic examination.

Down's syndrome newborn

Although the gestation periods are most often of normal length, the birth weight of infants with Down's syndrome is generally about one pound or so below the mean birth weight of normal newborns. One half of mongoloid newborns weigh less than six pounds. This finding accounts for the high rate of prematurity (estimated as high as 40% in mongolism) and the resulting increase of Down's syndrome infants in the premature nursery. The low birth weight for gestational age is associated with most of the other chromosomal anomalies and may be related to the retardation of growth rate in utero. The delay in growth continues in postnatal life, so that mongols are always small, generally being under the average height for their age, with few adults achieving much over five feet in height.

The newborn's face is frequently expressionless ("mongoloid expression"), and although the head circumference is generally within normal limits, the head is brachycephalic—shortened from the back to front measurement. The eyes are slanted upward at the outer sides, and there frequently is present bilaterally a fold of skin from the upper lid to the nasal bridge, called the epicanthic fold. The value of the finding of epicanthic folds as a diagnostic aid in Down's syndrome seems to be questionable, since a surprising 30% of normal newborns may have

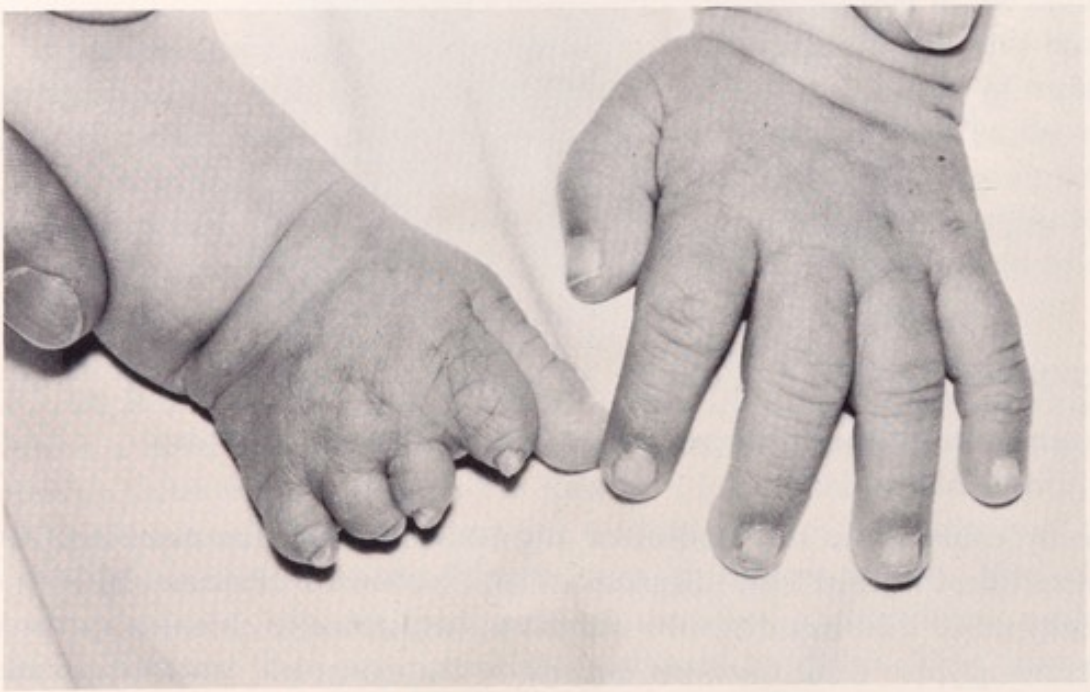

Fig. 6-4. Micromelia in a child with Down's syndrome. Various types of such birth defects are commonly found in Down's syndrome.

such a fold. Probably because of the dysplastic development of the skull, the eyes are relatively close together. A white speckling of the iris (Brushfield's spots) is found in a majority of Down's syndrome infants, although it is rare in Negro mongols; and there is an increased incidence of visual acuity defects, squints, and nystagmus. Although some observers have found an apparent tendency to blue or gray iris color, the percentage of brown-eyed mongols is not different from that of brown-eyed individuals in the normal population. (There is also no excessive incidence of color blindness later on among the mongoloid group.)

The nasal bridge is flattened; the nose is small and constantly filled with a mucous discharge. The tongue is constantly protruding, its size undoubtedly emphasized and exaggerated by the small mouth and the receding "Andy Gump" chin. The tongue may be furrowed; as the child grows older, it becomes increasingly fissured and shows hypertrophy of the papilla.

The ears are small, low-set, and positioned toward the back of the head. They are frequently rounded, very often displaying deformities of the helix and ear lobes. The skin may seem excessive for the skeleton, especially at the hands and wrists, and there may be folds of skin at the back of the neck. The hands and feet are short and broad, the fingers short and stubby. The little finger on each hand is especially short and curved in (clinodactyly), and a large gap is present between the first and second toes of the feet. The single transverse palmar crease (simian line) may be present on one or both hands, and the characteristic dermatoglyphic patterns described previously will be evidenced. Absence of one of the flexion creases on the little finger is a common finding. The poorly developed arches of the feet frequently lead to orthopedic problems later on in childhood. Other anomalies of the extremities, such as syndactyly and micromelia, may be present (Fig. 6-4).

In males, the penis and the scrotum may be tiny. The testes are permanently undescended in about one half of the boys. Even when descended, they are small and atrophic. The female may show large, cushionlike labia majora and underdeveloped labia minora. The pelvic abnormalities reflected by decreased iliac and acetabular angles on radiographic measurements (Fig. 6-5) are quite characteristic within the first year of life, but certainly should not be the sole diagnostic criterion since there is some overlap between normal and mongoloid measurements. There are very often many other associated anomalies in Down's syndrome. About one half of the children with Down's syndrome have congenital heart disease, primarily involving defects of the endocardial cushion. The most common anomalies are probably atrioventricularis communis and ostium primum, ventricular and atrial septal defects, patent ductus, and tetralogy of Fallot. Certainly a large percentage of the mortality (probably close to 50%) among Down's syndrome children in the first year of life is due to these heart defects. Other abnormalities of the gastrointestinal tract, such as duodenal atresia and Hirschsprung's disease, and of the genitourinary tract, such as renal agenesis, have also been reported as being increased in Down's syndrome.

The newborn child with Down's syndrome may not appear to be grossly ab-

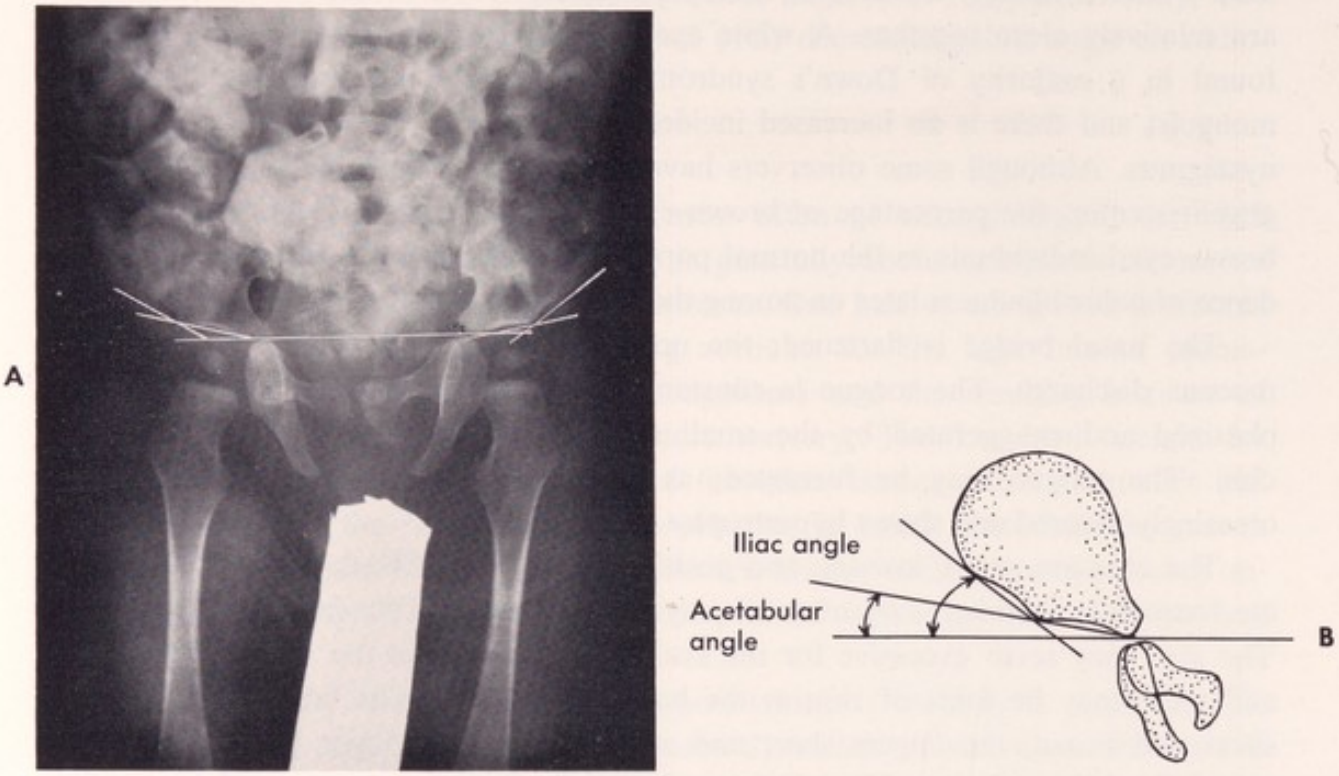

Fig. 6-5. A, Radiograph of the pelvis of a child with Down's syndrome and, **B,** a diagnostic sketch demonstrate narrow acetabular and iliac angles. These measurements are useful only up to approximately 3 months of age. (Courtesy Dr. Lawrence Davis, Louisville, Ky.)

normal in behavior. Unless there is an associated abnormality of some organ, the baby usually will present no special problems. The baby sleeps most of the time, feeds well, but often lazily. There may be a chronic problem of mucus, which will interfere with feeding. There are a generalized muscular flabbiness, lack of tone, and failure of normal responses to such stimuli as noises. The Moro reflex is commonly found to be absent.

GROWTH AND DEVELOPMENT OF THE CHILD WITH DOWN'S SYNDROME

All the abnormalities present at birth are indicative of the failure of normal prenatal development. The clinician who makes the diagnosis must be fully aware of the impaired way in which the child with mongolism will grow and develop during childhood and his early adult years. What are the potentialities for mental and physical development of the child with Down's syndrome? Certainly the mongoloid child will show some of the genetic endowment of the other members of the family, including his parents, so that there will be inherent variations even in mongolism. However, just as the lag in development is apparent at birth, a fairly predictable pattern of impaired future development can be explained to the parents early in the child's life.

The child will hold his mouth open habitually, probably due again to the small nasopharyngeal airways and the constant protrusion of the tongue. Rhinor-

rhea and respiratory infections are common in the newborn and neonatal period and may be secondary to the narrow passageway of the nasopharynx and the chronically enlarged tonsils and adenoid tissue. The deciduous teeth are invariably late in erupting, so that the first incisor's appearance may not be prior to the first birthday. Similarly, the completion of the deciduous dentition may not be present prior to 5 years of age, and permanent teeth will also have a delayed sequence of eruption. The teeth may be pegged; malocclusions are common, and periodontal disease is almost an invariable finding in Down's syndrome.

The voice is guttural and low-pitched. Although there are no specific abnormalities anatomically in the larynx, the articulation is very often faulty. Possibly this is due to the lack of controlled movements of the mouth, tongue, and lips.

In boys, the penis and testes (when descended) remain small. Axillary hair remains absent; the pubic hair may have a feminine escutcheon. Facial hair will also be scant and have a spotty distribution on the lower jaw. The male is generally considered to be sterile, and there have been no reports that a mongoloid individual has fathered a child.

The female's menarche will often be delayed, so that the majority of girls will not menstruate until after 18. Even then, the menstrual periods are irregular, the menopause occurring early, frequently in the thirties. Often the breasts will remain prepubertal in size, the enlargement, if any, being due to fat deposition.

"REGULAR" TYPE OF MONGOLISM, TRISOMY 21

The trisomy 21 type of mongolism occurs most often (in over 80% of the cases) in children born to women over 35 years of age. The evidence cited previously indicates that the extra chromosome is related to nondisjunction and increasing maternal age. There is some doubt as to whether the duplicated chromosome is actually the 21 or 22 chromosome, in fact as to whether duplication of either the 21 or 22 chromosome can produce the identical abnormality, but this problem is at present really one of semantics. Among children with Down's syndrome born to younger mothers, other types of cytogenetic abnormalities have been reported. However, the vast majority of these individuals are also of the trisomy 21 constitution.

TRANSLOCATION OR "FAMILIAL" MONGOLISM

A relatively small group of individuals with Down's syndrome (5%) show the normal number of chromosomes (46). The cells of these individuals do, actually, have extra chromosomal material, because of the attachment of the 21 chromosome to another autosomal chromosome. This abnormality is called *translocation* and essentially results in the formation of individuals with Down's syndrome resembling those of the trisomy (nondisjunction) type. However, because of loss of some genetic material during the fusion of the two chromosomes during translocation, there is not complete duplication of the 21 chromosome. Some dif-

ferences between the two types, biochemical and otherwise, may eventually be delineated. Translocation most frequently involves chromosomes of the 21 and the 13-15 groups (Fig. 6-6). Less commonly, the other small acrocentric chromosomes in the 21-22 group are involved. The etiology of translocation remains speculative, but the phenomenon may be due to chromosomal breaks and the resulting healing of the chromosome.

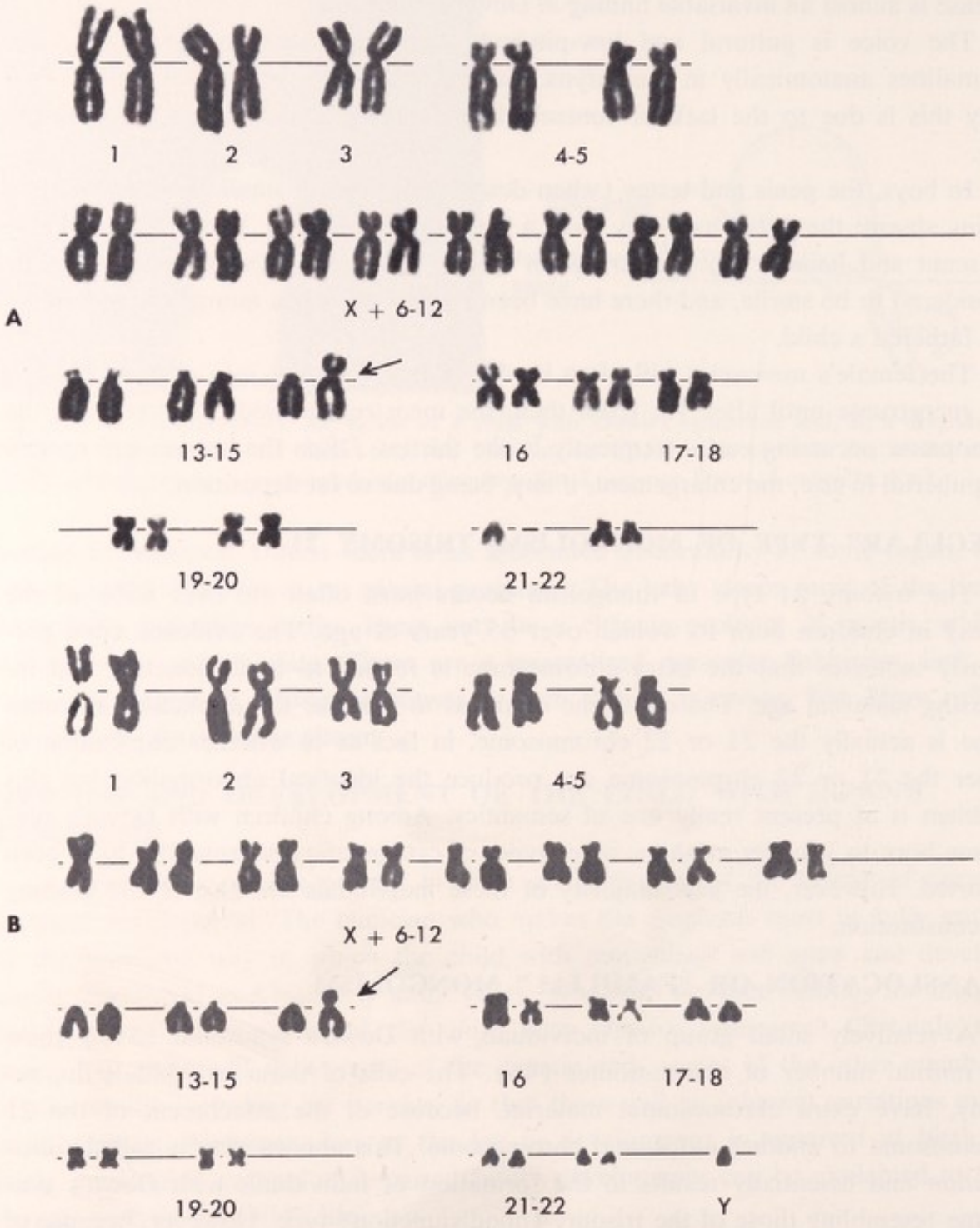

Fig. 6-6. Arrows indicate the translocation chromosome (21/15) in both the carrier mother, **A,** and the affected child, **B.**

In the translocation form of Down's syndrome, one of the parents may be a carrier of the anomaly. These parents are generally in the younger age group. The carrier has a normal phenotype (with no stigmata of Down's syndrome) but has a chromosomal complement of 45 chromosomes showing the abnormal translocation. Karyotypes of a child with a translocation Down's syndrome and his phenotypically normal but carrier parent are presented in Fig. 6-6.

The consequence of carrying the translocation is the eventual production of three types of zygotes. (Certain combinations of abnormal gametes would be lethal.) Theoretically, one third of the live offspring would be normal, one third of them would be phenotypically normal but translocation carriers like the parents, and one third of them would have Down's syndrome of the translocation type. Reports now indicate that when the mother carries the translocation, there are approximately equal numbers of normals, carriers, and cases of Down's syndrome. There are also frequent abortions. If the father is a carrier, the vast majority of the children are normal or carriers, and offspring with mongolism are rarely reported. It is thus apparent why many familial cases of Down's syndrome will be of the translocation type. Identification of the carrier parent in young parents of mongoloid children is of vital importance in genetic counseling.

The discovery of persons with double chromosome abnormalities, for example, Down's syndrome–Klinefelter's (XXY) or Down's syndrome–triple X, and of families with individuals with different cytogenetic abnormalities, may indicate that disjunctional accidents are not purely random in the population. The recurrence of trisomy mongolism in families may be due to a heritable tendency to nondisjunction. It is certainly possible that there is a genetic susceptibility (certain mutant genes increasing the rate of production of chromosomal errors such as Down's syndrome). In at least one half of the families producing two or more individuals with mongolism, there is no evidence of mosaicism or translocation to explain the recurrence of the defect.

MOSAICISM

Mosaicism is the condition in which there may be tissues with different chromosomal constitutions. In Down's syndrome mosaicism, there will be an admixture of normal cells and cells with 47 chromosomes, with trisomy of number 21. Frequently, chromosomal mosaicism for the mongol chromosome is associated with only a few manifestations of the disease. In fact, the mental development of these individuals has varied from severe retardation to complete normalcy. We have studied a child with mosaic chromosome patterns who had a much higher intelligence than the average child with Down's syndrome. He is shown in Fig. 6-7. This child's IQ was 86, certainly in the low-normal intelligence group, and he had only a few stigmata of Down's syndrome, including epicanthal folds and a depressed nasal bridge. Many of the previously mentioned borderline individuals with only a few signs of mongolism may be similar mosaics. The importance of the individual with mosaic Down's syndrome is that he may appear clinically nor-

Fig. 6-7. Child with trisomy 21/normal chromosomal mosaicism. The choice of reading material is his own. (From Reisman, L. E.: G. P. **34**:172, 1966.)

mal yet have an abnormal cell line in either his somatic or germ cell tissues. Thus, both in translocation Down's syndrome and in mosaic mongolism, normal-appearing persons may carry the abnormal chromosome and pass it to their offspring. Mosaicism probably results most frequently from an abnormal cell division during early embryonic development.

DOWN'S SYNDROME AND LEUKEMIA

Individuals with Down's syndrome have a marked susceptibility to leukemia. Acute leukemia is seven to fifteen times as frequent in children with mongolism as in the general population. It would seem reasonable to argue that the aneuploidy (abnormal chromosome number) in mongolism, with its inherent genetic imbalance, may be related to the predisposition to leukemia. There is a significantly increased occurrence of mongolism in children who have siblings with leukemia. Again, as in the previously mentioned double trisomy syndromes, there may be some parallel genetic predisposition to both disorders.

REPRODUCTION IN MOTHERS WITH DOWN'S SYNDROME

There are now a small number of cases in which women with Down's syndrome have had children (Fig. 6-8). Some mongoloid women have ovulatory

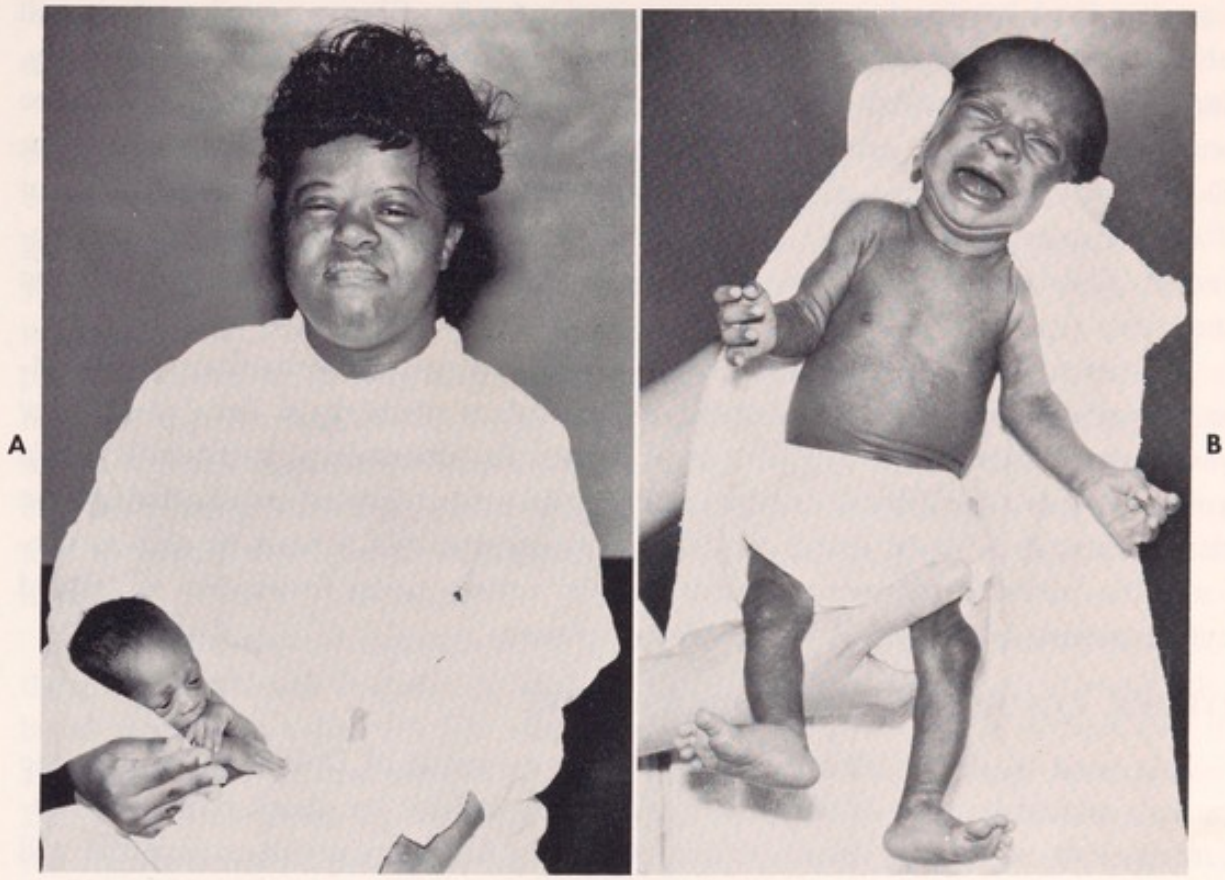

Fig. 6-8. Mother, **A,** has a trisomy 21 chromosome constitution. The infant, **B,** is normal cytogenetically. Although males with Down's syndrome are sterile, some females can obviously reproduce. (From Tagher, P., and Reisman, L.: Obstet. Gynec. **27:**182, 1966.)

menstrual cycles and are capable of reproduction. Of the offspring studied cytogenetically, about half have been individuals with Down's syndrome and half have been unaffected. This 1:1 ratio indicates that half the eggs produced by the woman with Down's syndrome receive the extra chromosome and half do not. This is called secondary nondisjunction. The eggs with the extra number 21 chromosome give rise to offspring with Down's syndrome. Men with Down's syndrome are apparently unable to reproduce. Those who have been studied have had no sperm, or grossly subnormal amounts of sperm.

GENETIC COUNSELING

The young mother with a mongol child is naturally very much concerned that the anomaly may occur again in a subsequent child. If the affected child is of the regular trisomic 21 type (and the parents are chromosomally normal), the mother under the age of 35 has only a slightly increased risk of having more affected children than other women of the same age in the random population. About one fifth of mothers of children with Down's syndrome are in the younger age group. This group is termed maternal-age–independent, and it is these mothers who should be subjected to chromosomal analysis. Some of these individuals will be of the translocation type. In these cases, the physician can accurately estimate the chances

(as described previously) of recurrence in the family. Chromosomal analysis will also determine, or exclude, the possibility of chromosomal mosaicism. Similarly, families with a second birth of a child with Down's syndrome should be studied. It has been estimated that approximately 5% of all individuals with Down's syndrome have the translocation type. Of these translocations, about 70% have arisen de novo, and the parents have normal chromosome complements. The recurrence risk in this group is similar to that in parents of trisomic mongols.

In view of the increasing knowledge of basic cytogenetic mechanisms, the genetic counselor's advice is less empiric today than it might have been just a few years ago. Chromosome studies are necessary for counseling, particularly when young parents are involved or when siblings and other relatives are affected. In the near future, it is hoped that most clinical laboratories will at least be able to perform the initial chromosome procedure, the results being forwarded to trained cytogeneticists in medical centers for interpretation.

OTHER COUNSELING CONSIDERATIONS

As soon as the physician is aware of the diagnosis of Down's syndrome, the parents should be told. Most parents are unprepared for the shock of having a retarded child, so the physician's role in explaining the many problems involved will be a difficult one. The family physician will have two immediate problems: first, deciding what to tell the parents, and then helping the parents decide whether or not to place the child in an institution.

The physician's approach in informing the parents of the diagnosis when the child is still in the hospital is usually to tell the father first. Then the physician or the father tells the mother prior to her seeing the baby. At this point, the diagnosis of Down's syndrome may be the only information given to the parents. Many physicians may apprise the parents of the concomitant mental retardation found with this syndrome, but practices seem to differ in the extent to which physicians stress varying degrees of mental retardation possible. During the initial counseling, we have found it most important to have families understand the diagnosis and the inevitability of some retardation. Unless the child is obviously very seriously damaged, it does not appear reasonable to dwell on any exact degree of retardation except in general terms. Too often, zealous physicians have emphasized a prediction that the child will never walk, talk, or develop any self-help abilities and have been surprised to find in later years that the child was not that severely retarded. Errors in the other direction are just as common.

What the physician can emphasize is that most of the children with trisomy 21 are in the moderately retarded range of intelligence (IQ's from about 30 to 50), with some children being more severely retarded (IQ below 30) and some children having abilities at the higher end of the mildly retarded range (IQ's from 60 to 70). The physician can further indicate that children with the mosaic form of Down's syndrome have been found to have even higher intellectual potential.

As we indicated earlier, some such children can have low-normal to normal intelligence.

In counseling parents with a mongoloid infant, it is also important for the physician to give the parents some expectations about the child's developmental course for the first year or so of life. Motor development in these children is generally comparable with the progress of normal children up to about 2 to 3 years of age. In the first 6 months of life motor development may even appear completely normal. Parents not aware that the mongoloid child has such a normal pattern of motor development may interpret these developmental successes as evidence that the diagnosis of Down's syndrome was erroneous. Sometimes parents may continue to accept the diagnosis, but believe that because of his motor prowess, their mongoloid child, unlike others, will not be retarded. If the parents are told to expect this kind of development, they are not so likely to entertain false hopes.

It is in the area of language development that the parents will be provided with the greatest evidence that their child is different. Language acquisition is usually delayed more than other abilities and may, in some cases, provide a handicap in addition to the general degree of retardation. Delays in language development should be anticipated by the parents so that their attempts to teach language to the child will not be premature and consequently unrewarding. Speech therapy and special language training are not of value during these early years.

All of the advance information given by the physician can help the parents to arm themselves for the unexpected and to view this particular child from a new frame of reference. The difficulties faced by these parents can then be placed in the context of what problems can be reasonably expected in having such a child. Very adequate parents may feel like abject failures in dealing with their mongoloid child when their expectations and subsequent actions are based on standards exacted from experiences with normal children.

Counseling given to parents of the mongoloid child should also broach another subject: the efficacy of medication for amelioration of the mental retardation. No doubt many parents will ask about or know of claims that drugs have raised the IQ levels of mongoloid children. The physician MUST be aware of the literature on this matter. Much of the discussion about positive results from studies on these drugs is controversial, but, to date, there appears to be no evidence that IQ's of mongoloids can be raised by medication alone. Some of the side effects of such studies, such as increased attention paid to the children and more exposure of the children to experienced supervision, have produced better socialization and better learning readiness of mongoloid children. These effects, however, are a result of better environmental conditions, not of medication.

Better environmental conditions for the mongoloid child and adult do pay handsome rewards. It is for this reason that the physician who gives advice concerning institutionalization should be very thoughtful about his recommendations. As a general rule, mongoloid children who are kept at home, encouraged to par-

ticipate in normal family life, and exposed to training experiences in special classes do much better, physically and mentally, than those children placed in institutions. The home-reared mongoloid's social adjustment as an adult and his readiness to take some productive place in society are improved accordingly. It must be understood, however, that this is a general rule. The physician must take into consideration the strengths and weaknesses of the family, the institutions available, and the child. Specifically, he should consider the emotional, financial, religious, and educational resources of the family and the degree of retardation of the child. Also, he should be aware of the quality, admittance requirements, and the waiting list of the institutions.

The physician can explore these considerations about institutionalization with the family, but, at the same time, he should refrain from indicating his approval or disapproval of the family's decision. The counselor might think it a wonderful thing for a family to rear a severely retarded child in the home—but if he gives manifest approval of the choice to keep a child at home and the parents change their minds, they are not likely to feel free to return to him for help.

The best approach for counseling parents about institutionalization is to give them the advantages and disadvantages of placing a child out of the home, point out the concrete steps necessary to placing a child in an institution, and then indicate that, whatever their choice, we will help them in their endeavors. Moreover, it is most important that a sincere indication of our continued interest be made to the parents. That interest may and perhaps should include more counseling sessions.

In addition to institutionalization, the physician can consider alternate plans for maintaining the child out of the home. Placement of the child in a foster home or in a private residential setting may be acceptable to some parents. Temporary placement in some situations has been found helpful when the parents' resources are so strained that they need relief from caring for the child at home. Older children can be managed for part of the day in day care centers, special schools, and special classes so that the mother can gain some respite.

As we have mentioned before, counseling about most mongoloid infants should not concentrate on specifics regarding the mental abilities of a particular child. When the child gets older, however, or when a child is diagnosed as mongoloid at a later age, efforts should be made to obtain precise information about the child's mental abilities. After about the age of 2 to 3 years, intelligence testing of mongoloid children is quite reliable, and the predictions afforded by IQ scores should be included in the counseling. If possible, a complete evaluation, such as provided by mental retardation or birth defects centers, should be made. In general, the specialists on the interdisciplinary teams of these centers will be able to give the parents useful information about the child's general intelligence, language and speech abilities, and social skills. Guidelines for the parents' management of the child are usually given along with the clinical information, and in many cases the parents are given specific programs to follow: placement in nursery school, speech therapy, etc.

The counseling given to parents at mental retardation and birth defects centers should be considered an extension of the family physician's counseling. Unfortunately, in some cases, family physicians use these centers to get rid of their counseling obligations; in other cases, the centers themselves make little effort to include the family physician in their counseling efforts. In these instances, the parents may get confusing and sometimes conflicting information that can be harmful to the understanding and plans needed for the mongoloid child. Ideally, one would like to see specialty centers and family physicians maintaining a continuous dialogue between themselves and with the parents. Happily, this approach is being promoted in most communities where specialty centers are located.

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Chapter 7

Autosomal chromosome abnormalities and the "funny looking kid" syndromes

In addition to Down's syndrome, there is a fairly large group of disorders and syndromes that are associated with gross errors of chromosomal makeup. Like Down's syndrome, these disorders display certain specific features that make them readily diagnosable at the bedside, or, to be more precise, at the rails of the nursery crib. Either duplication of genetic material (as in the trisomy syndromes) or loss of significant amounts of certain chromosomes (as in the deletion anomalies) often gives rise to a characteristic phenotype, depending upon the chromosome involved. We will discuss here the clinical disorders associated with the well-defined autosomal chromosome anomalies. (The sex chromosome aberrations will be discussed in the next chapter.) We will also describe several children seen in our own clinic who have some other, but less common, abnormalities. The descriptions are given in order to help the physician decide when to ask for chromosomal examinations; this chapter is not intended as an encyclopedic volume on cytogenetic abnormalities.

The "funny looking" aspect of these children, as the term is applied in the title of this chapter, relates to the peculiar facial features and skeletal malformations that bring them to the physician's attention. Careful scrutiny of the face, the hands and feet (including the dermatoglyphic patterns), and other physical features may lead to a clinical diagnosis. For example, hands with fingerlike thumbs are frequently associated with congenital heart disease (Fig. 7-1). This combination is known as the Holt-Oram or "heart-hands" syndrome, or atriodigital dysplasia, that apparently has a dominant mode of inheritance. Another association, that between odd-shaped ears and renal anomalies, is one of the older "pearls" of clinical medicine.

Most of these syndromes have a genetic basis. For that reason, the physician should extend his search for diagnostic signs to include other family members. Therefore, it is important to see the other members of the family, especially both parents, at some time during the patient's work-up. The diagnosis in the new-

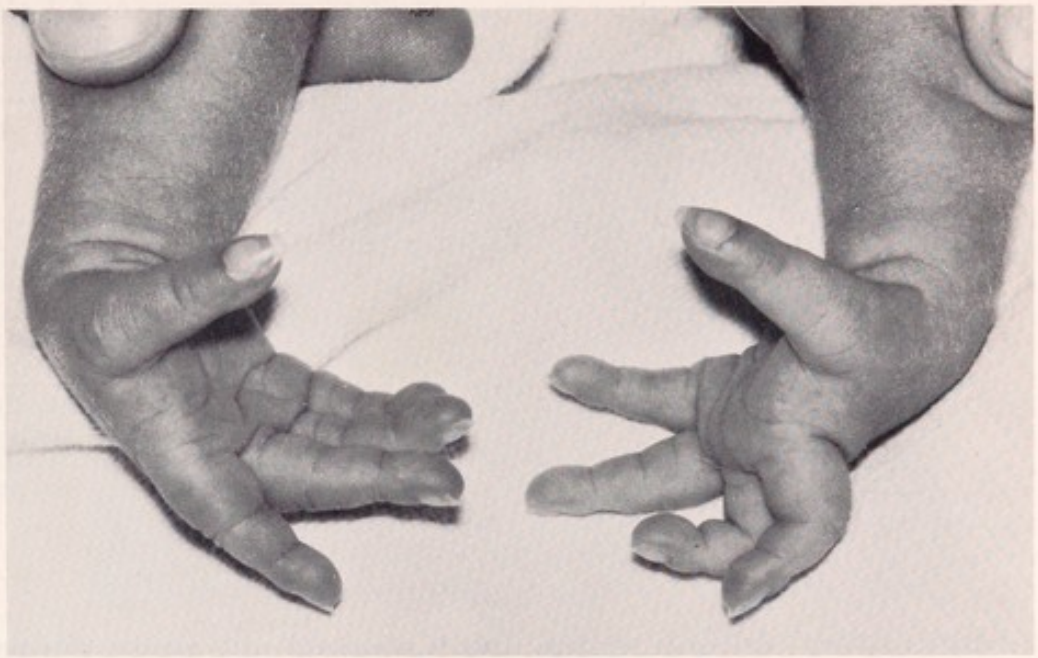


Fig. 7-1. Fingerlike thumbs associated with congenital heart disease in a young infant. This syndrome is transmitted in an autosomal-dominant manner.

born child whose hands are shown in Fig. 7-1 was certified when the parents were interviewed. The father had identical fingerlike thumbs and had been followed in the cardiac clinic with a diagnosis of atrial septal defect. It is interesting to note that very often it is the relatively minor anomalies that are of the greatest help diagnostically.

Most frequently, however, these children have nonspecific facial and skeletal anomalies, such as epicanthal folds, small mandibles, beaklike noses, dental anomalies, micrognathia, high-arched palate, or hypertelorism. The infants may have peculiar flexion deformities of the fingers or "rocker bottom" feet (Fig. 7-2). It might be informative to include the "funny smelling" infants (the musty odor of the phenylketonuric's diapers has often been the initial clue in the detection of this disease) or "funny crying" infants in this same group. The latter would, of course, be typified by the patients with Cri du chat syndrome, whose kitten-like cries are so characteristic—but even then, this cry must be differentiated from the weak, high-pitched efforts of the newborn with other types of brain damage. Almost always, the common denominator existing among all these "funny looking kids" seems to be the presence of mental and psychomotor retardation, and a failure to thrive.

It is apparent that, just as in Down's syndrome, there are very few specific pathognomonic abnormalities for each of these syndromes. In fact, there is considerable overlap of diagnostic signs among these syndromes. For example, the transverse palmar crease (simian line), low-set ears, and high-arched palate may be found in the individual children affected in all the "funny looking syndromes" we will discuss. For this reason alone, it is a difficult task to relate specific mal-

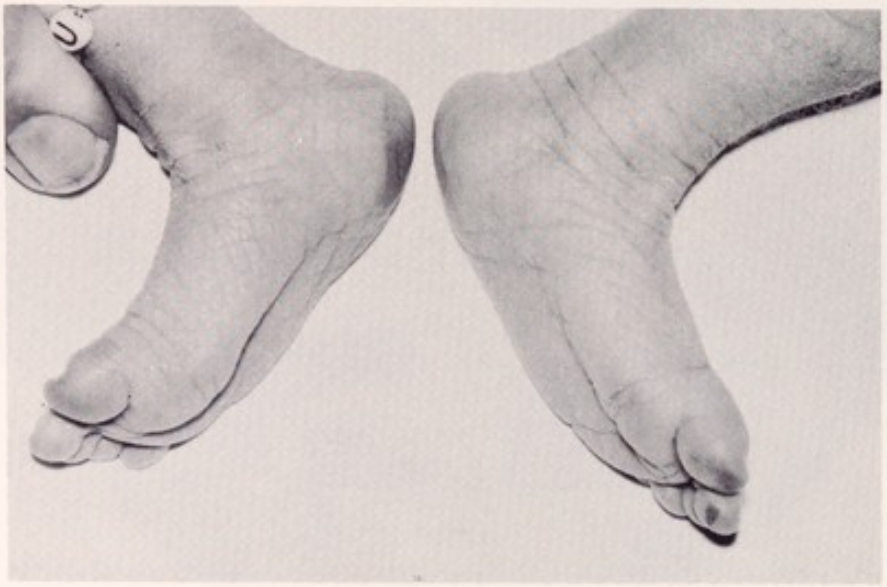


Fig. 7-2. "Rocker-bottom" deformity of feet. This is associated with various chromosomal abnormalities.

formations and specific "funny" characteristics to definite chromosomal segments that are lost or duplicated.

It also seems appropriate for us to include some material in this chapter on the "funny looking kids" for whom chromosomal abnormalities are not found, but who most often do represent genetic alterations or mutations, rather than alterations in entire segments of chromosomes.

AUTOSOMAL TRISOMY SYNDROMES OTHER THAN DOWN'S SYNDROME

Nondisjunction of the number 21 chromosome during meiosis results in Down's syndrome. During the same meiotic process occurring in either sperm or egg, a similar error may befall other chromosomes, resulting in trisomy syndromes. The effects of nondisjunction of the sex chromosomes are discussed in the next chapter. The two autosomal trisomy conditions that have now been established as distinct clinical entities are trisomy D_1 (13-15) and trisomy E (18). The phenotypic abnormalities that are most constantly related to these syndromes are listed in Table 7-1.

D_1 AND E TRISOMY SYNDROMES

The D_1 trisomy syndrome was first recognized as a chromosomal abnormality by Patau and associates in 1960, but the arrhinencephalic complex of abnormalities associated with it had been described by clinicians in the nineteenth century. The arrhinencephalia (involving absence of the olfactory bulbs and tracts associated with maldevelopment of the frontal lobe of the brain) is perhaps the most specific of the anomalies characterizing the disorder. Yet the phenotypic pattern of malformations

Table 7-1. Abnormalities in the D_1 and E trisomy syndromes

	D_1 trisomy	*E trisomy*
Head	Shallow supraorbital ridges with sloping forehead; microcephaly; defects in cranial bones	Prominent occiput
Eyes	Microphthalmus; retinal dysplasia; colobomas of iris; narrowed palpebral fissures	Protruding eyes; epicanthal folds
Ears	Malformed, low-set	Malformed, low-set
Mouth and mandible	Cleft lip; cleft palate; high, arched palate; receding chin	Receding chin; high-arched palate
Hands and feet	Simian lines; polydactyly of hands and feet; rocker-bottom feet; flexion deformities of fingers with retroflexible thumbs; dysplastic nails; syndactyly	Single crease on fifth finger; simian lines; flexion of fingers, characteristically index finger over third finger; rocker-bottom feet; dorsiflexion of big toes
Cardiac	Dextroposition and interventricular septal defects are most common of the congenital heart defects	Most common defects are patent ductus arteriosus and intraventricular septal
Renal	Hydronephrosis, often due to bladder neck obstruction	Horseshoe kidney; duplication of ureters
Abdominal	Incomplete rotation of colon; omphalocele; umbilical and inguinal hernias	Eventration of diaphragm; heterotopic pancreatic tissue; hernias
Genitalia	Cryptorchidism in males; bicornuate uterus in females	Cryptorchidism in males
Skin	Diffuse capillary hemangiomas, especially on forehead, nape of neck, and lower back	Mottled skin; lanugo-like hair on back and extremities
Neurologic	Severe psychomotor and mental retardation; apneic spells; arrhinencephalia and malformations of brain, especially frontal region	Marked rigidity and muscular hypertonicity; spina bifida and meningomyelocele; brain deformities; seizures

of the D_1 trisomy, like the pattern for Down's syndrome, is readily recognizable at birth (Fig. 7-3).

The incidence of D_1 trisomy is reported to be about one in 2,500 newborns, and there is a great female preponderance among the affected newborn infants. The birth weight is frequently low for the gestational age, and the infants are generally in difficulty from the time of birth. It is likely that most of the D_1 trisomy embryos are lost as abortuses, as suggested by the finding that a large number of abortus tissues studied cytogenetically have been reported as being D or E trisomies. Those infants surviving the in utero period usually live only a few days or weeks; yet a handful of such patients have been known to survive for several years. Whatever the length of life, these children are severely or

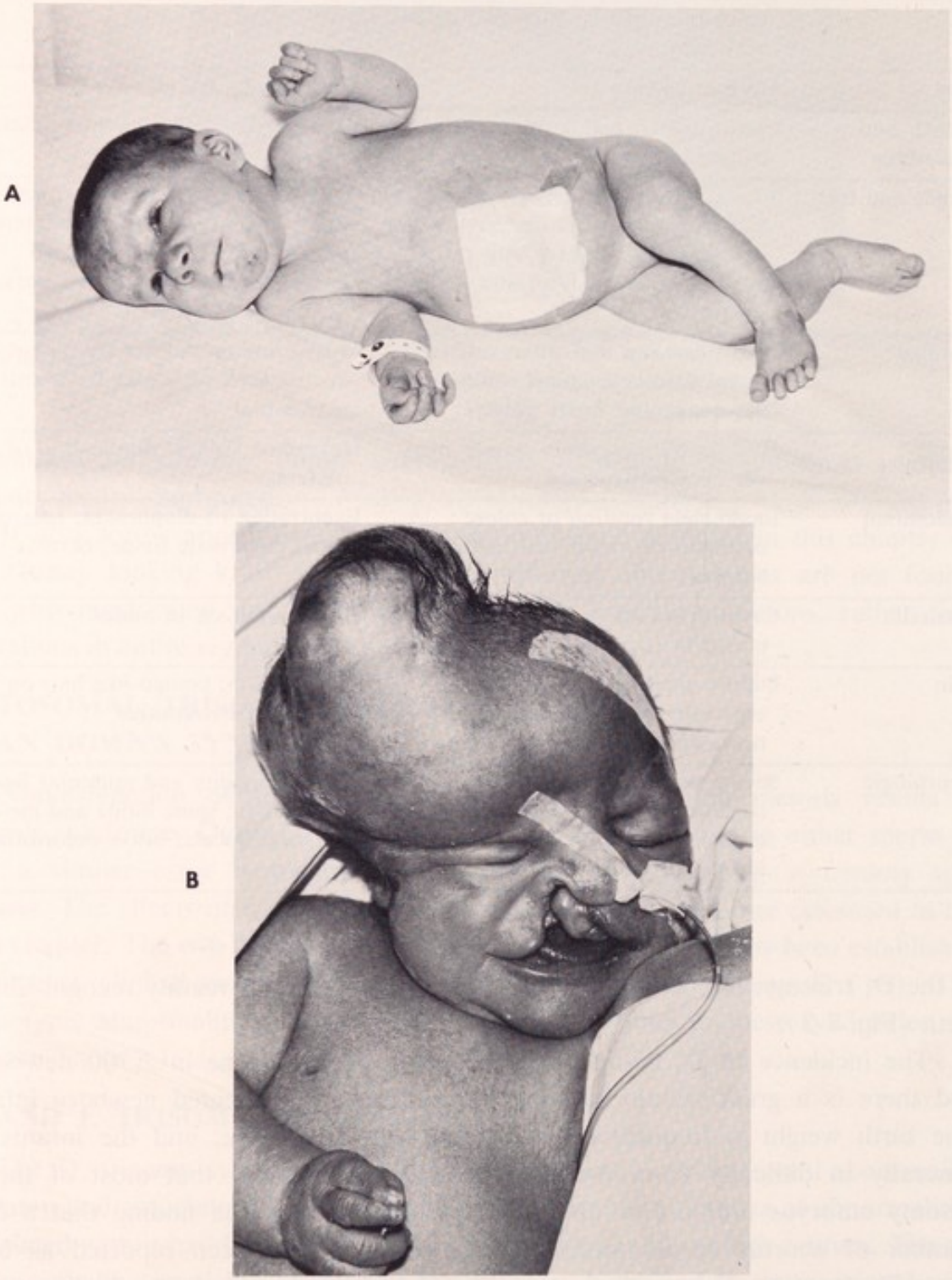


Fig. 7-3. Infants with D_1 trisomy syndrome displaying, **A,** sloping forehead, microphthalmos, low-set ears, receding chin, and, **B,** cleft lip and encephalocele. (**A,** From Murphy, J. W., Singh, S., and Reisman, L. E.: J. Kentucky Med. Ass. **65:**585, 1967.)

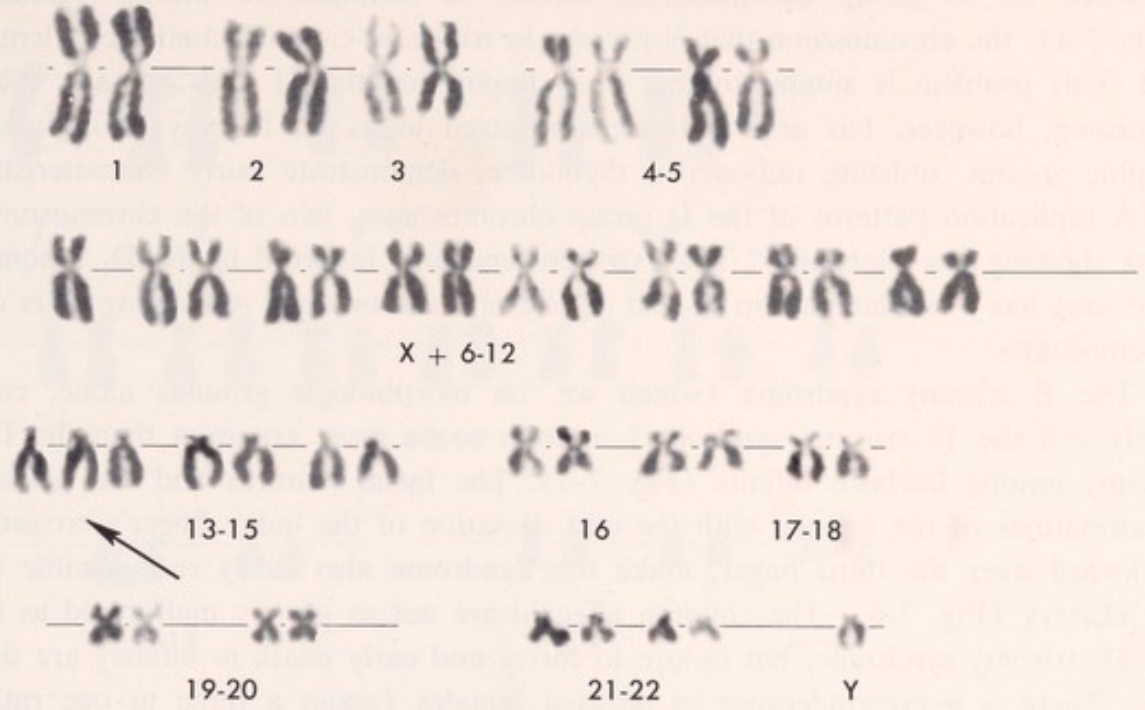


Fig. 7-4. Karyotype demonstrating D_1 trisomy. The extra chromosome in the 13-15 group, arrow, is indistinguishable morphologically, but may be identified by using autoradiography.

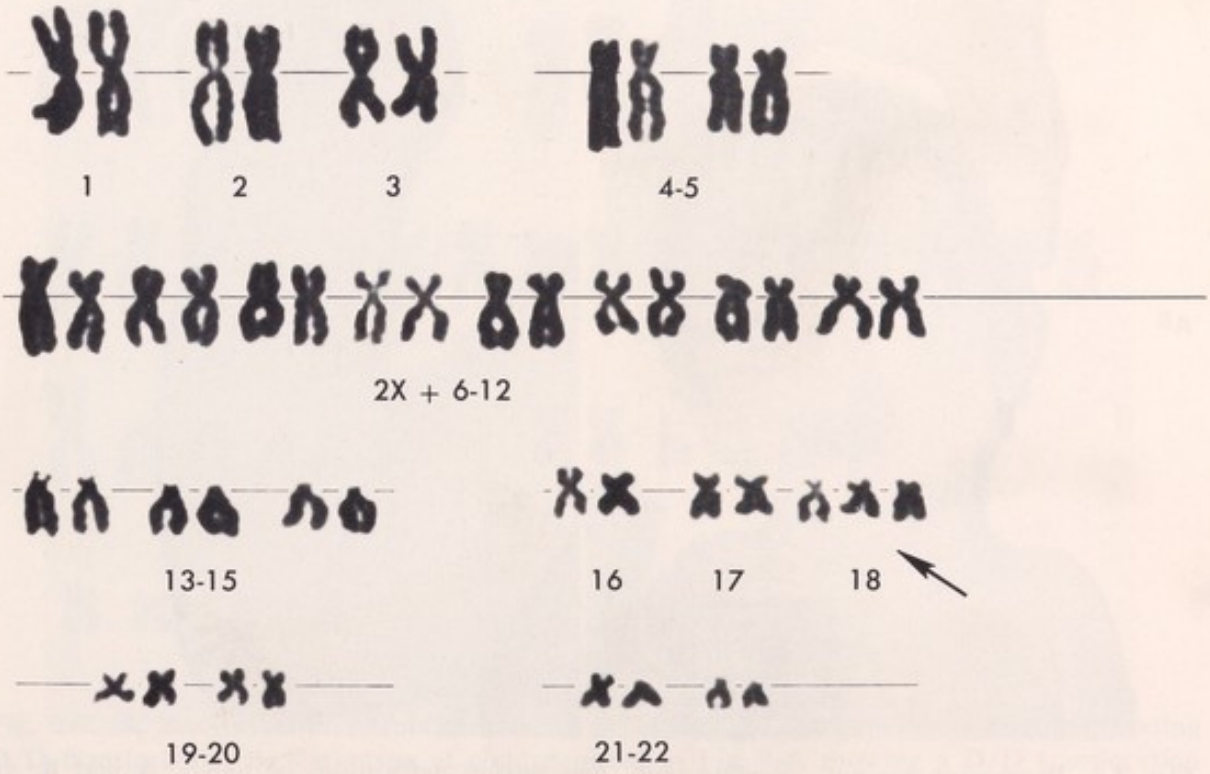


Fig. 7-5. Karyotype of 18 (E) trisomy abnormality.

profoundly retarded. The specific cause of death often may not be clear, since there are multiple physical abnormalities, including cardiac and brain defects. Any one of these abnormalities is potentially lethal to the affected infants.

Since the D group chromosomes cannot be distinguished morphologically (Fig. 7-4), the chromosome that is present in triplicate cannot actually be identified. This problem is similar to that of distinguishing the 21 and 22 pairs. The syndrome, however, has arbitrarily been referred to as D_1 trisomy. Autoradiographic studies, utilizing radioactive thymidine, demonstrate fairly characteristic DNA replication patterns of the D group chromosomes, two of the chromosome pairs showing late "labeling." The extra chromosome involved in the D_1 trisomy syndrome has a similar pattern to that of one of these two late replicating pairs of chromosomes.

The E trisomy syndrome (which we, on morphologic grounds alone, can safely call the 18 trisomy syndrome) appears to be more common than the D_1 trisomy among liveborn infants (Fig. 7-5). The facial features and the flexion abnormalities of the fingers, with the odd deviation of the index finger's crossing backward over the third finger, make this syndrome also easily recognizable in the nursery (Fig. 7-6). The children affected are not as grossly malformed as in the D_1 trisomy syndrome, but failure to thrive and early death in infancy are the rule. There is a preponderance of affected females (about a three to one ratio

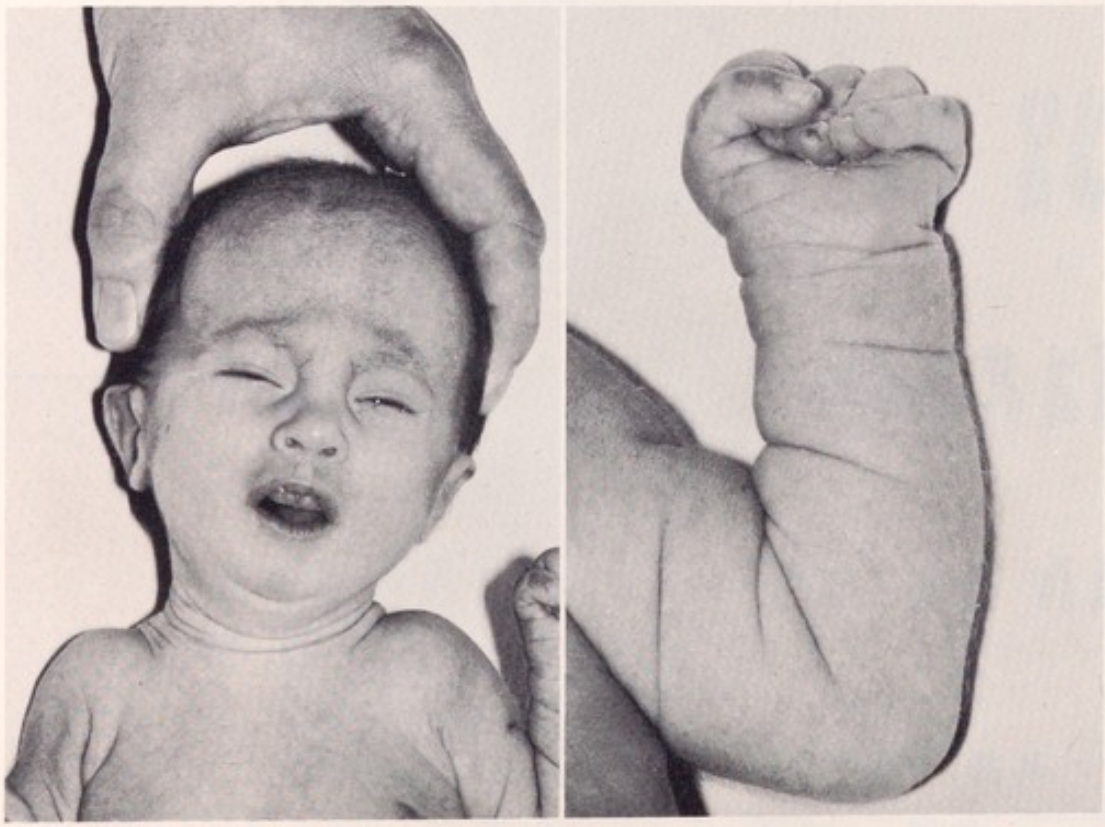


Fig. 7-6. Prominent occiput, receding chin, and flexion deformities of hands, **A** and **B,** are classical findings in 18 trisomy syndrome.

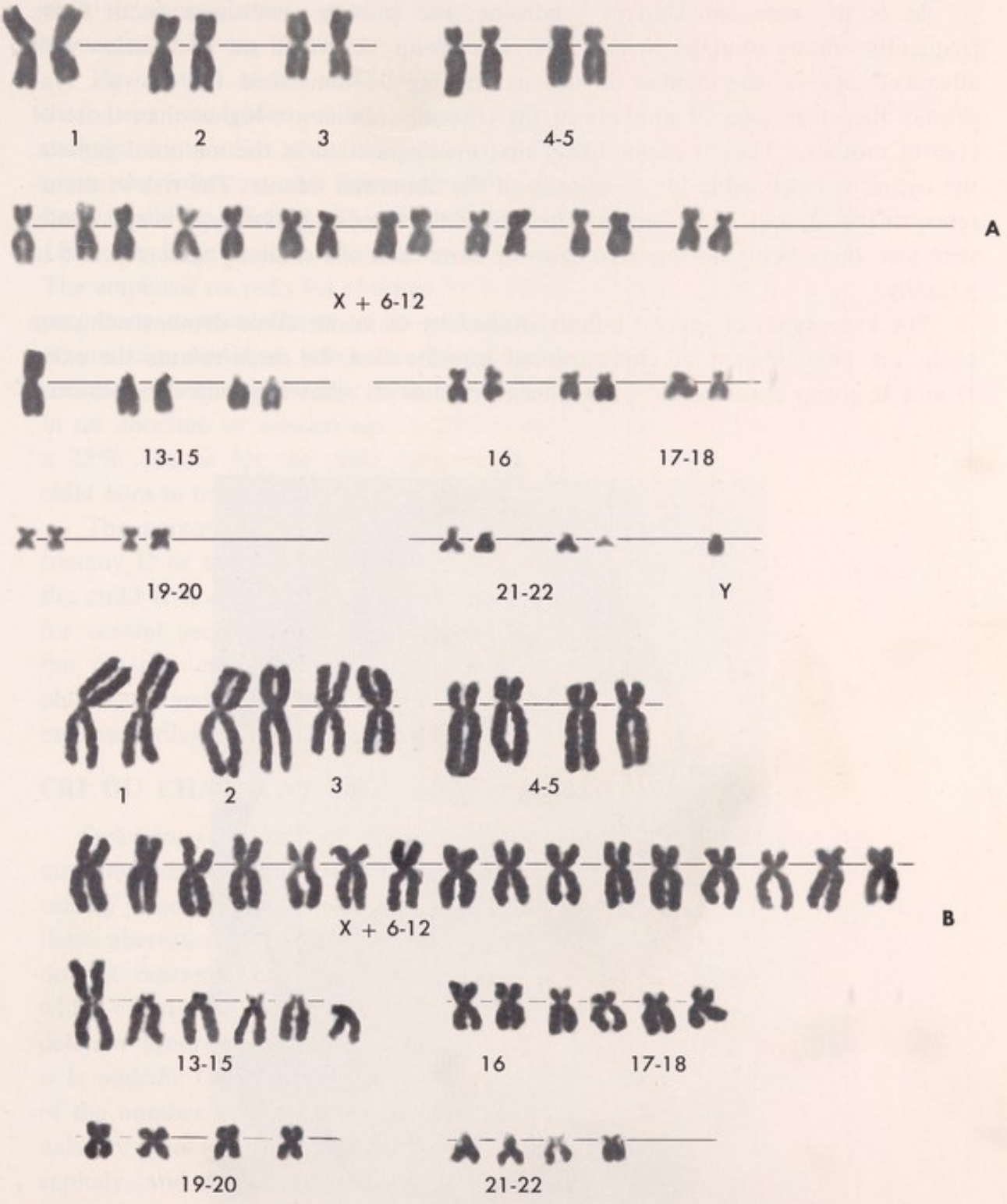


Fig. 7-7. A, Karyotype of phenotypically normal father of child in Fig. 7-8, demonstrating D/D translocation. **B,** Karyotype of child depicted in Fig. 7-8, showing a D/D translocation type of D_1 trisomy syndrome.

over males), as there is in the D_1 trisomy syndrome. This sex pattern may reflect an increased lethality for the XY individual, as opposed to the XX individual, in utero.

Counseling considerations

As is the case for Down's syndrome, the trisomy syndromes occur more frequently among mothers in the older age group. Although the correlation with advanced age of the mother is not as striking as that cited for Down's syndrome, the mean ages of mothers of the trisomic infants are higher than those of control mothers. Thus it seems likely that nondisjunction in the maternal gamete, the ovum, is responsible for a majority of the abnormal infants. The risk of recurrence of the D_1 and 18 trisomy syndromes of the nondisjunction type is apparently very low, there being no reported cases of more than one similarly affected child in a family.

The karyotypes of several infants studied by us in our clinic demonstrate once again the phenomenon of chromosomal translocation. In these infants the extra D and E group chromosomes have been attached to other D group chromosomes

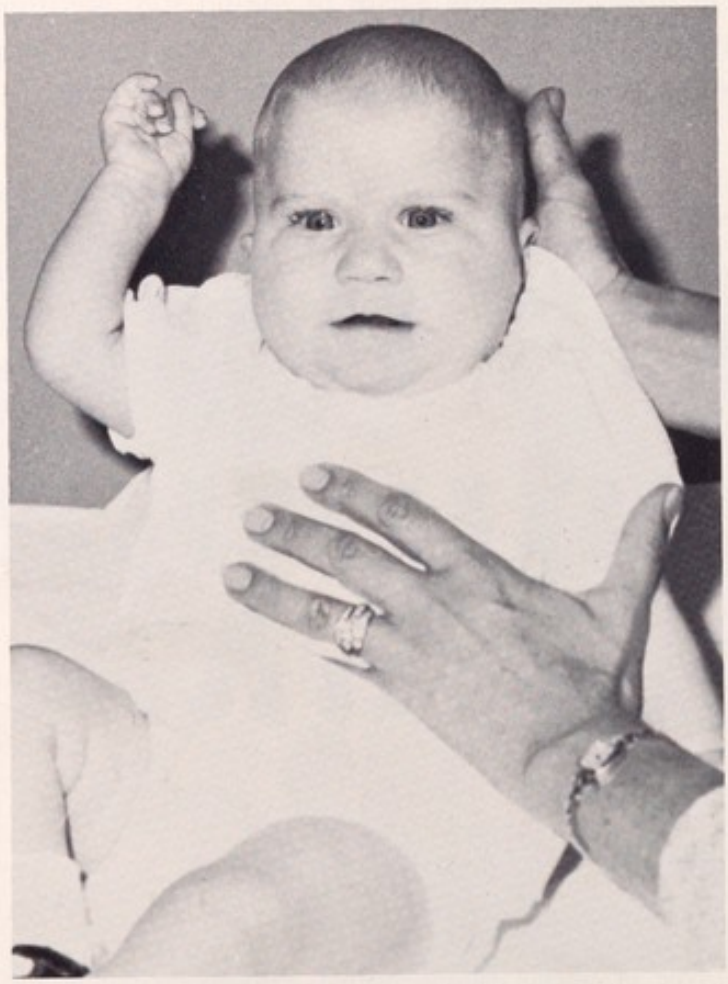


Fig. 7-8. Child with D/D translocation. Note the facial resemblance to the infant in Fig. 7-3, **A.**

(as in the translocation types of mongolism). These translocation errors can occur de novo, but in a good number of cases one of the parents may be a balanced carrier (as in the figure) of the chromosomal abnormality (Fig. 7-7). The risks of translocation carriers, as discussed previously, represent one of the more pressing reasons for the study of chromosomal patterns of the parents of children with multiple abnormalities, or of children who have died very early in infancy and are suspected of having had one of the chromosomal syndromes.

The mother of the child depicted in Fig. 7-8 had had one miscarriage, and there was one older sibling with an apparently normal karyotype. The autoradiographic studies were indicative of a 13/14 translocation, so that one could quote the following risk figures to the parents: 33⅓% risk that the next child born would be affected, 33⅓% risk that the next child born would be a carrier (like the father), and 33⅓% risk that the next child born would be normal. The emphasis on risks for children *born* indirectly reflects the risks for the mother's pregnancy to terminate in an abortion or miscarriage. Appoximately 25% of these pregnancies would so terminate. Therefore, if we give risk figures based on pregnancies rather than births, there is a 25% chance that a pregnancy will result in an abortion or miscarriage, a 25% chance for the child *born* to be affected, a 25% chance for the child *born* to be a carrier, and a 25% chance for the child *born* to be normal.

The parents should also be told of the poor prognosis for a child with the trisomy D or trisomy 18 syndrome. Even with the best medical and nursing care, the child is not likely to survive the neonatal period, and even if he does survive for several years, he will be profoundly damaged. By giving this information to the parents, one might be able to prevent their shopping around for different physicians and institutions. They should certainly be helped to avoid pursuing expensive diagnostic and surgical procedures.

CRI DU CHAT (CAT CRY) AND DELETION SYNDROMES

Deletion (or loss) of chromosome material is associated with mental retardation and multiple congenital anomalies. The loss of a chromosome segment usually occurs during meiosis, so that an abnormal zygote is produced. Most of these aberrations involving loss of a small amount of an autosomal chromosome do not represent clear-cut clinical syndromes. Instead they seem to produce a wide variety of congenital abnormalities and stigmata. One fairly constant deletion syndrome (described by that great clinical observer, Jerome Lejeune) is *la maladie Cri du chat,* the cat-cry syndrome. A major portion of the short arm of the number five chromosome (as shown in Fig. 7-9) is deleted. These individuals are also marked by profound mental retardation, a failure to thrive, microcephaly, and a characteristic "moon" face. Their cry as an infant is the most dramatic feature of the syndrome. The babies have a weak, high-pitched, mewing-like cry resembling that of a cat or, more precisely, young kittens. There does not seem to be a specific anatomic laryngeal abnormality to explain the cry, which is

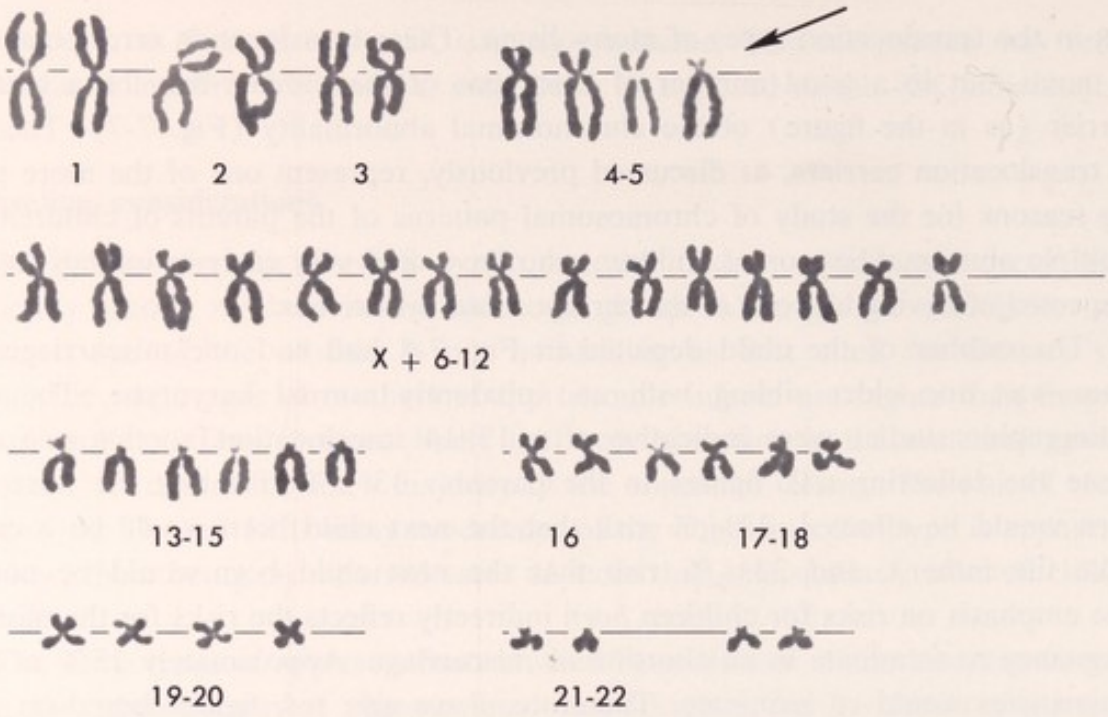


Fig. 7-9. Karyotype illustrating a deletion of part of the short arms of chromosome number 5, arrow, characteristic of the Cri du chat syndrome.

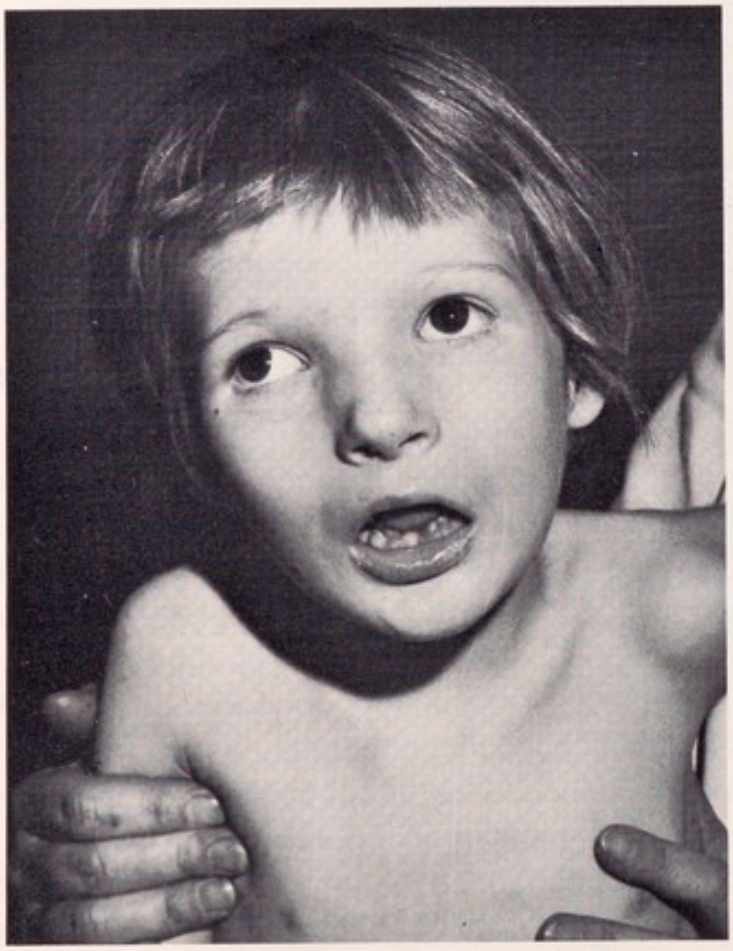


Fig. 7-10. Child with Cri du chat syndrome. Note the "moon" face, hypertelorism, and micrognathia.

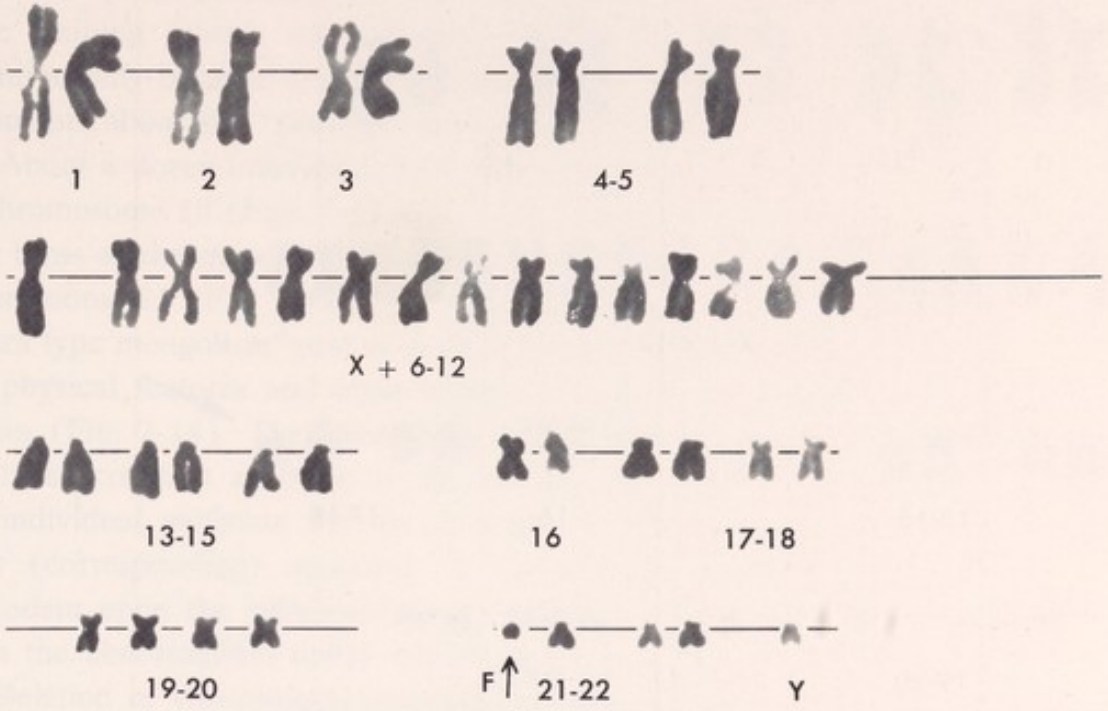


Fig. 7-11. Deletion of the short arms of chromosome 18 is indicated by the arrow.

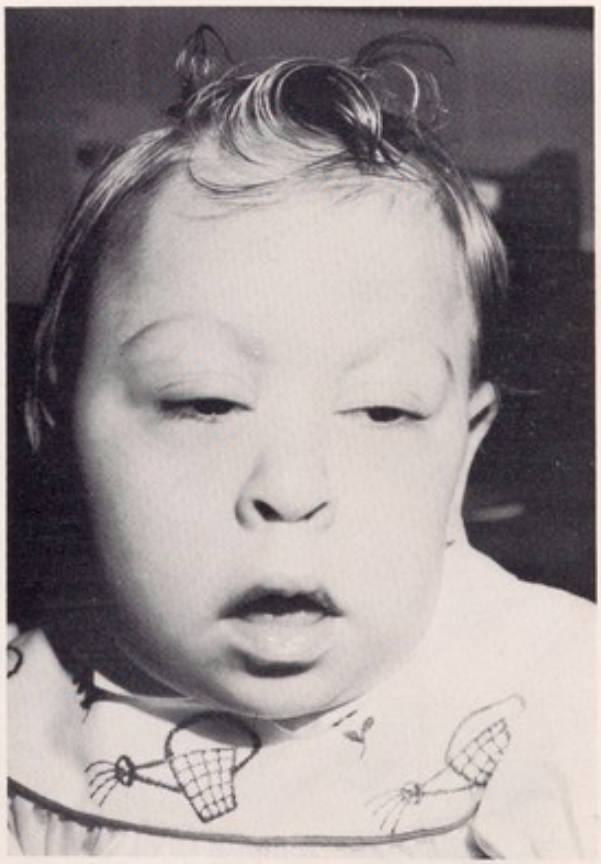


Fig. 7-12. An 18-month-old infant who had convulsive seizures and profound retardation. An autopsy indicated that the corpus callosum was absent.

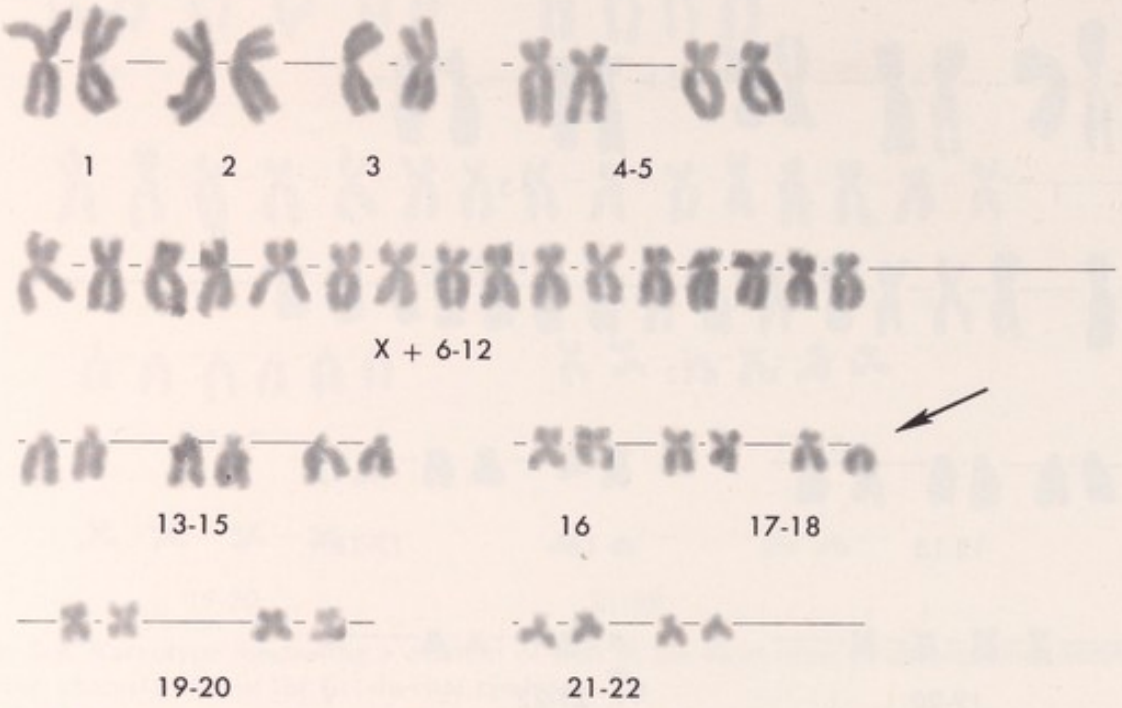


Fig. 7-13. Deletion of a great part of chromosome 21 is indicated by the arrow.

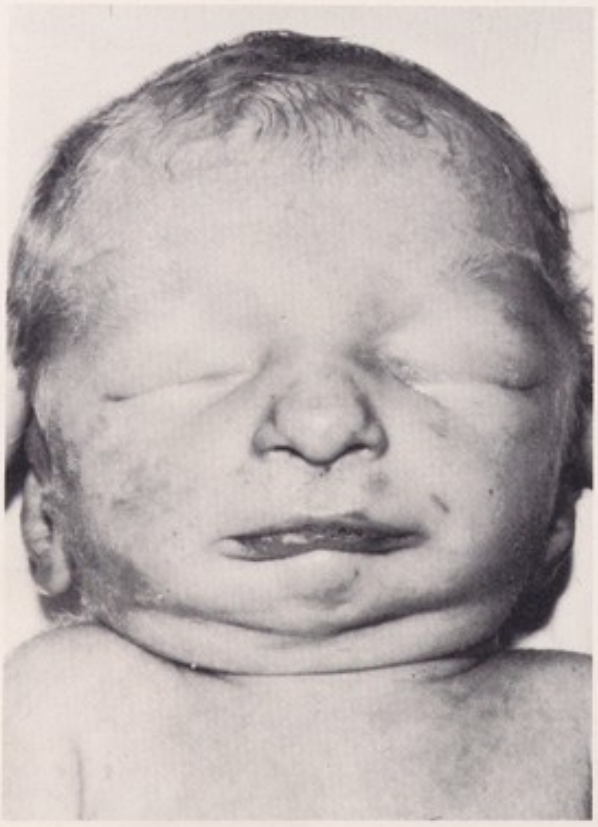


Fig. 7-14. An "antimongol" child who had thrombocytopenia, pyloric stenosis, hypertonia, and many congenital abnormalities. There was a marked failure to thrive. (From Reisman, L. E., Kasahara, S., Chung, C-Y, Darnell, A., and Hall, B.: Lancet **1**:394, 1966.)

not present in the older child. Laryngomalacia has been observed in some infants with this syndrome. We have seen a 6-year-old girl, presently hospitalized in the state training school, with the characteristic syndrome. She first came to our attention only because a social worker's report included a notation of the mother's comments about the "peculiar" way the child cried in infancy (Fig. 7-10).

About a dozen individuals have been described with deletion of the short arms of chromosome 18 (Figs. 7-11 and 7-12), another small group with deletions of the long arms of chromosome 18, and several children with losses of a great deal of the chromosome 21 (Fig. 7-13). The latter syndrome was described by Lejeune as "le contra type mongolism" and soon after by us as "antimongolism," because many of the physical features and abnormalities seemed to be opposite to those of mongolism (Fig. 7-14). The phenotypes of the deletion syndromes, however, are not nearly so constant as those of the trisomy syndromes. This may be because of the individual variation due to exposure of recessive genes by loss of homologous (corresponding) segments of chromosome material. Thus, varying traits dependent upon the individual's own hereditary background may be superimposed upon the abnormalities solely related to the loss of a bit of chromosome.

Deletion of chromosome segments is likely due to breaks in the chromosome at various distances from the centromere. If broken ends heal together (in

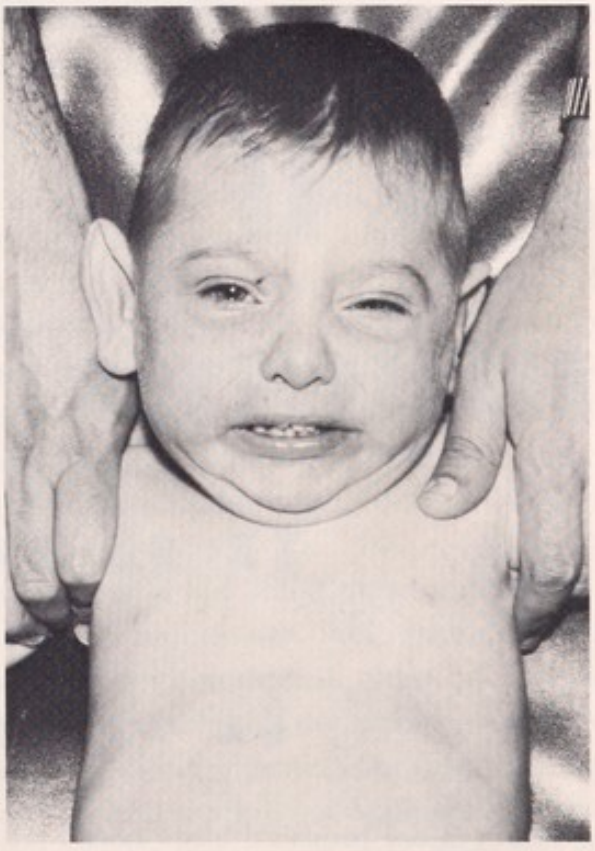
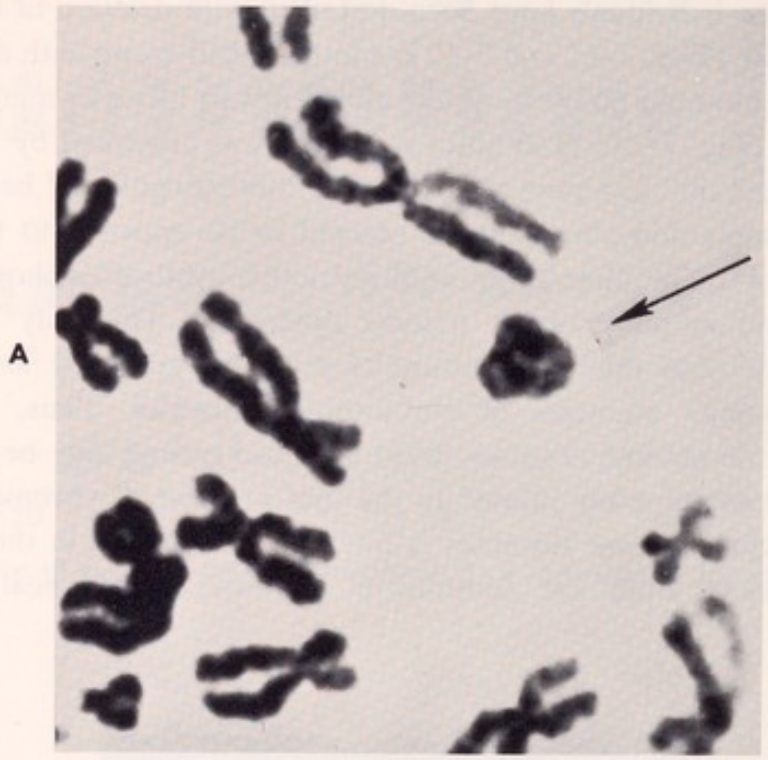


Fig. 7-15. Child with a ring D chromosome abnormality. (From Reisman, L., Darnell, A., and Murphy, J.: Lancet **2**:445, 1965.)



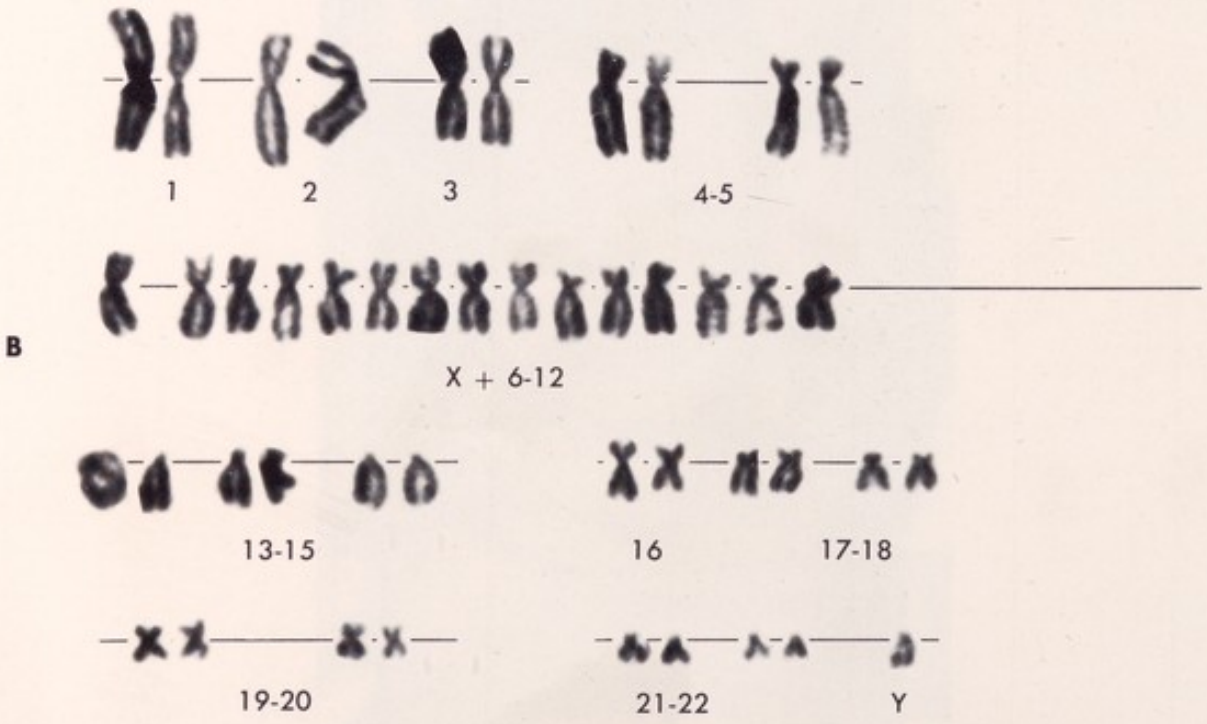


Fig. 7-16. A, Ring form, arrow, in one peripheral blood culture metaphase figure. **B,** Karyotype showing the replacement of a normal D group chromosome by the abnormal ring chromosome.

fruit fly genetics, we know that broken ends are notoriously "sticky"), a ring chromosome may be formed. The child pictured in Fig. 7-15 was severely retarded and had an imperforate anus, hypospadias, and several other relatively minor congenital defects. Analysis of his peripheral blood leukocytes and of his skin cultures revealed a ring chromosome, which represented a D group chromosome that had undergone breakage, and then reunion of the broken ends (Fig. 7-16). An exciting aspect of our clinical and cytogenetic investigations of this child was the absence in his serum of any measurable haptoglobin, which, we believe, might be related to the missing piece of chromosome. This raises the possibility that specific gene loci may be lost during chromosomal breakage. The potentialities of such gene mapping may be a very significant part of the future studies in human genetics.

The most important aspect of our studies, as far as the young parents of the child were concerned, was our explanation of their child's abnormalities and our advice to them for having other children. Since a chromosome analysis had revealed that the parents' leukocytes were normal, we could reasonably assure them that their child with the ring D chromosome indeed represented a bizarre and unusual meiotic accident. The chances for recurrence of this abnormality (or another chromosomal error) were relatively remote.

Normally, the chromosomes (and chromatids) divide longitudinally after chromosome replication. Occasionally, they divide transversely and result in abnormal chromosomes that are composed of equal arms, both of which have the same genetic content. Most of the reported cases of this type of aberrant division (isochromosomes) involve one of the X chromosomes in the female.

OTHER "FUNNY LOOKING KID" SYNDROMES

As we indicated earlier, not all children with syndromes depicted by odd or unusual malformations are found to have autosomal or sex chromosome anomalies. Despite the absence of chromosomal signs or clear-cut evidence for inheritance, the "funny looking kid" syndromes are of interest in clinical genetics. For one reason, the occurrence of one of these syndromes in a family presents diagnostic questions that generally touch upon aspects of heredity. For another reason, genetic hypotheses have been advanced for most of these syndromes. Very often they seem to be related to a multifactorial inheritance, rather than to a classically dominant or recessive pattern.

The seemingly minor facial and hand abnormalities are invariably associated with other congenital abnormalities—in fact, generally with multiple anomalies. They make up a host of syndromes that often have no specifically recognized etiology or heredity. We are not able to blame a single defective gene, as we can in achondroplasia or cystic fibrosis, nor can we clearly detect a carrier or carriers of the trait. Instead there is an apparent interrelated etiologic involvement of at least several genetic factors and of in utero and neonatal environmental factors. Frequently, such things as age, sex, and skin color of the affected in-

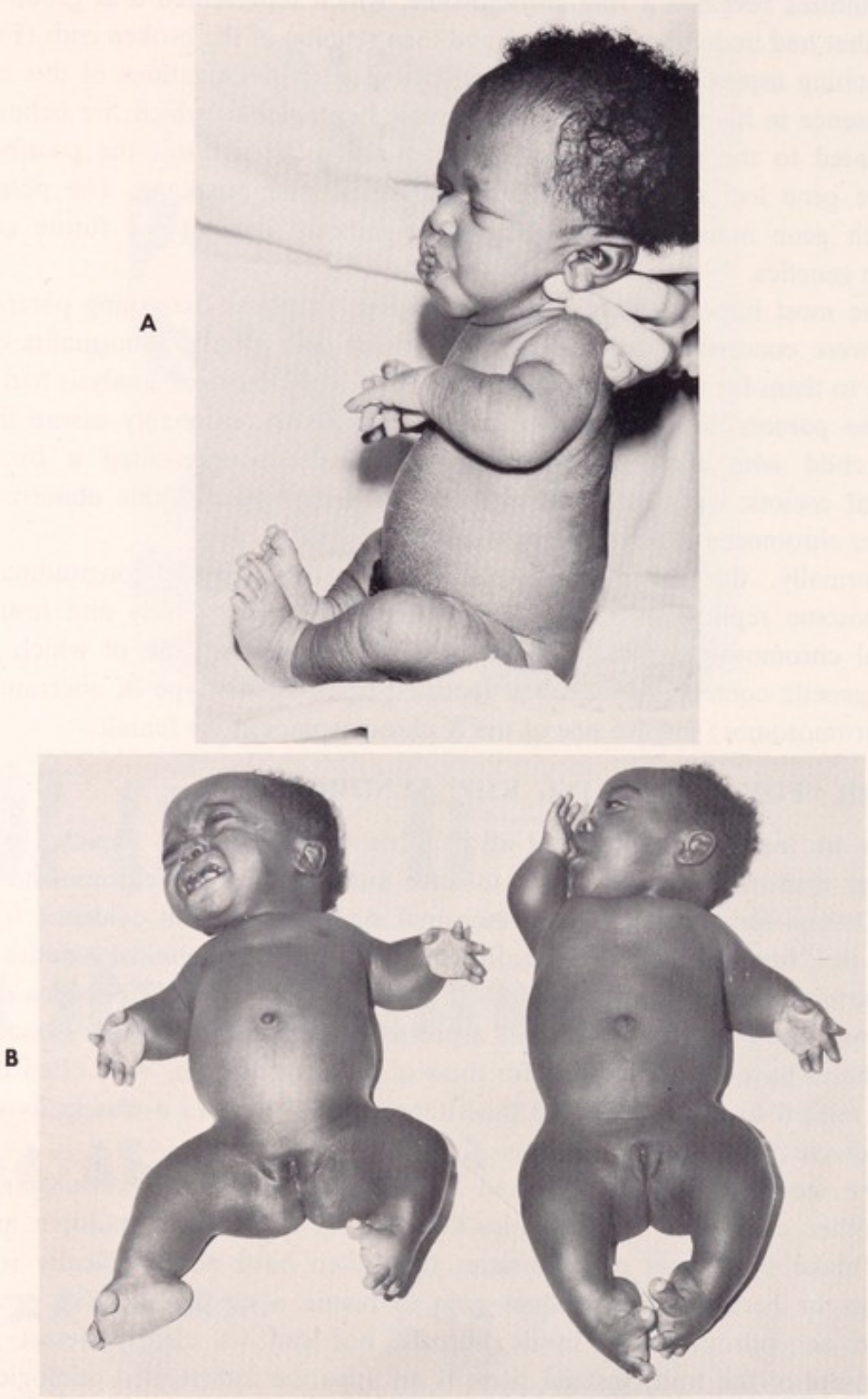


Fig. 7-17. A, Achondroplastic dwarf demonstrating marked shortening of the extremities. **B,** Monozygotic twins, diastrophic dwarfs, who have associated bizarre skeletal abnormalities.

dividuals have a bearing on the course and outcome of the disease. We will discuss some of the individual malformations, such as cleft palate, pyloric stenosis, and syndactyly, later in this book. The "funny looking kid" anomalies (not related to the specific chromosome errors we discussed previously), however, almost always present similar problems as to the genetic prognosis we can offer the affected families. Our counseling is limited to empiric data, such as presented in actuarial tables of life insurance companies. Mendelian rules of inheritance cannot be used.

It is important to make a clinical diagnosis in individuals with these syndromes involving multiple abnormalities, because of the different genetic risks inherent in the family, and because of the varying prognoses regarding mental abilities, growth, and the like. In Fig. 7-17 we illustrate two types of dwarfism: achondroplasia, which has a dominant mode of inheritance, and diastrophic dwarfism, which may be inherited as an autosomal-recessive. Phenotypic differentiation of these two types of dwarfism is based on the bizarre deformities of the hands, feet, and other skeletal abnormalities that are present in the diastrophic (or "twisted") dwarfs. The differential diagnosis is vital because of the different prognoses that must be given to the young parents of the children affected. In addition to illustrating a different mode of inheritance, the individuals with the diastrophic form of osteochondroplasia are much more severely handicapped. Other conditions, mostly genetically implicated, that involve dwarfism accompany some of the syndromes given in Table 7-2.

One of these syndromes for which dwarfism is a fairly constant feature is the so-called Hallerman-Streif syndrome. The Hallerman-Streif syndrome consists of birdlike facies, congenital cataracts, scanty hair (especially of scalp and eyebrows), hypoplastic mandible, and a proportionate dwarfism (Fig. 2-3). Because of the sporadic nature of this disease, and its rarity, we can reassure a mother that recurrence of the anomaly is very unlikely. But since this syndrome has been described in siblings, and, in fact, in monozygotic twins, we cannot be positive that "lightning will not strike twice." We can more confidently assure the parents that their affected child's mental abilities are normal at the time of examination.

On the other hand, identification of the child with Rubinstein-Taybi syndrome (broad toe–broad thumb anomaly), depicted in Fig. 7-18, enabled us to give a necessarily pessimistic (but at least accurate) prognosis to the parents. When the child was 8 years old, the parents had been told only that she would be a little slow, but they had no idea that her potential as a member of the family and community would be limited. We could not give advice about empiric risks to the parents because the sparsity of reported cases, together with the rare report of reproduction in affected individuals with this and similar syndromes, makes the exact pattern of heredity uncertain.

As we have observed, the mongoloid facies is highly characteristic. The same is true of the facies in some of the other chromosomal anomalies, such as in the *Cri du chat* and the D_1 trisomy syndromes, and in the nonchromosomal syndromes we have grouped under "funny looking kids." Besides aberrant traits or stigmata—

Table 7-2. "Funny looking kid" syndromes

Syndrome	*Heredity*	*Facial characteristics*	*Associated abnormalities*
Hallerman-Streif (dyscephaly with congenital cataract and hypotrichosis)	Multifactorial (described in homomonozygotic twins)	Face is small, birdlike; widely patent fontanelles; congenital cataract; hypoplastic mandible; hypotrichosis; dental anomalies; blue sclerae	Dwarfism; syndactyly (normal intelligence)
Rubinstein-Taybi (broad toes and broad thumbs syndrome)	Only sporadic cases reported thus far, but probably multifactorial	Antimongoloid slant of eyes; beaked nose; small mandible	Retardation; frequent infections; short, broad thumbs and toes; cardiac abnormalities
Orodigitofacial dysostosis (OFD syndrome)	Described only in females; probably a sex-linked dominant; may be lethal in males	Cleft tongue; pseudocleft in upper lip; hyperplastic frenulum; cleft palate (1/100 cases of cleft palate are OFD syndrome)	Syndactyly, other anomalies of hands; mental retardation is associated in a number of cases
Cornelia de Lange syndrome	Multifactorial; reported in several families	Heavy eyebrows meeting in midline; general hirsutism; antimongoloid eyes; low-set ears; arched palate	Severe retardation; micromelia; syndactyly; skeletal defects; congenital heart disease
Bird-headed dwarf of Seckel (primordial dwarfism)	Multifactorial; reported in siblings	Microcephaly; beaklike nose and preponderance of central portion of face; antimongoloid slant of eyes; hypoplastic mandible	Dwarfism; mental retardation; hypotonicity skeletal anomalies; anomalies of genitalia
Robin's syndrome (Pierre Robin)	Multifactorial; apparently involves maldevelopment of first arch area	Micrognathia, cleft palate and glossoptosis; "Andy Gump" appearance	Mental retardation in 20%; hydrocephalus; congenital heart disease
Crouzon's (craniofacial dysostosis)	Autosomal-dominant	Craniostenosis with microcephaly, exophthalmos; beaked nose; mandibular prognathism	Syndactyly; optic atrophy; simian lines; mental retardation
Apert's (acrocephalosyndactyly)	Autosomal-dominant (may have varying penetrance)	Craniostenosis with oxycephaly; exophthalmos	Syndactyly varying in degree to true osseous fusion; mental retardation
Idiopathic infantile hypercalcemia (associated with supravalvular aortic stenosis)	Multifactorial; vitamin D sensitivity?	"Elfin" face; small skull (craniostenosis); epicanthic folds; strabismus; a retroussé nose; underdeveloped mandible; wide mouth	Hypotonia; hypercalcemia; dwarfism; mental and psychomotor retardation; heart disease

Table 7-2. "Funny looking kid" syndromes—cont'd

Syndrome	*Heredity*	*Facial characteristics*	*Associated abnormalities*
Progeria (Hutchinson-Gilford syndrome)	No hereditary pattern described	Small face; appearance of newly hatched bird; alopecia; ears small; nose beaked; small mandible	Dwarfism; death due to old age and coronary disease in teens; osteoporosis
Hemihypertrophy (Silver's syndrome)	Multifactorial; reported in several generations	Involves all the facial structures, *including* teeth	Associated with increased incidence of Wilms' tumor; hemihypertrophy of one side of body, including internal organs
Ellis-van Creveld (Chondroectodermal dysplasia)	Autosomal-recessive (25% of patients have affected siblings)	Sparse scalp and eyebrow hair; fusion of upper lid to gingival margin; natal teeth; abnormal dentition	Polydactyly; acromelic dwarfism (distalward shortening of extremities); congenital heart defects; mental retardation

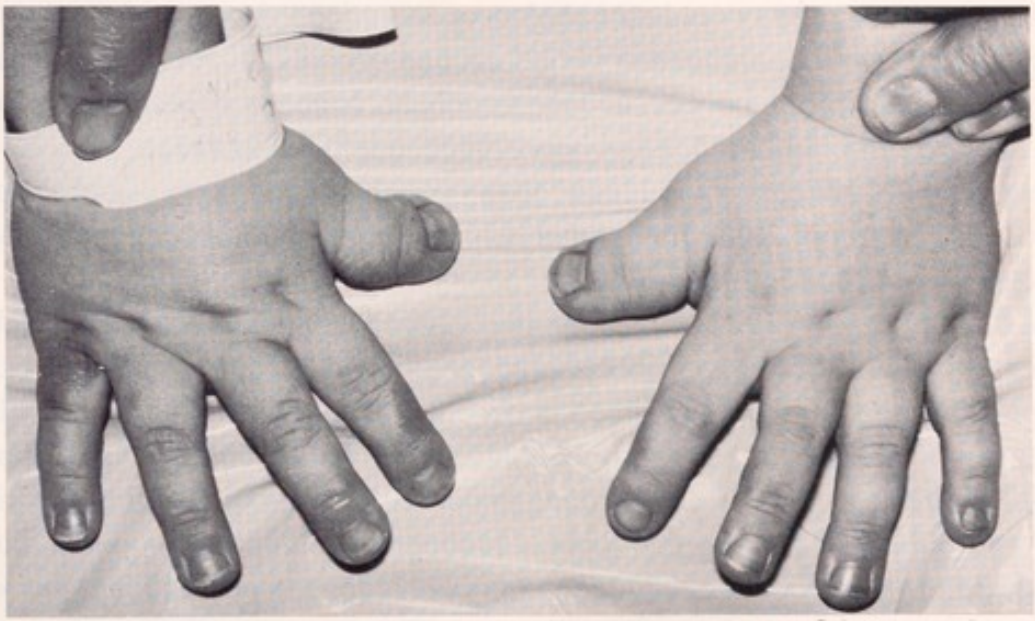


Fig. 7-18. Broad thumbs associated with mental retardation.

the craniofacial dysplasias, transverse palmar lines, malformations of the ears—we do find some common denominators among the individuals with the various sorts of autosomal chromosome errors. These common characteristics include a low birth weight for gestational age, a failure to thrive and generalized growth retardation, and psychomotor or mental retardation. This commonality makes us believe that the physical and developmental abnormalities are little related to the loss of specific

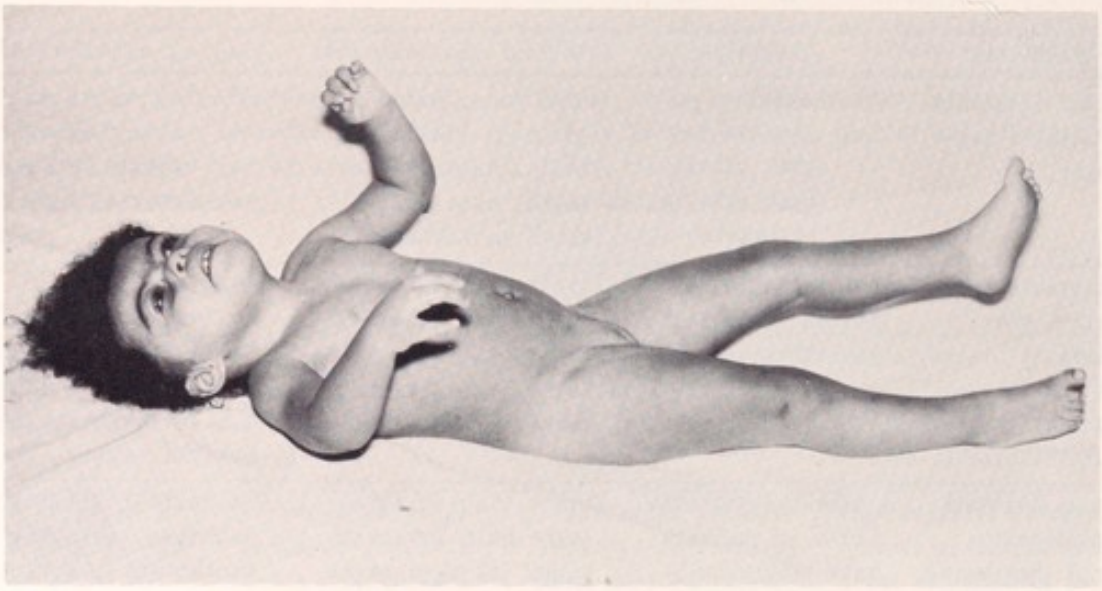


Fig. 7-19. Profoundly retarded child with marked hirsutism and skeletal abnormalities associated with Cornelia de Lange syndrome.

genes during the complex chromosome rearrangements. Instead, these chromosomal or genetic imbalances may lead to imbalances in various tissues and organs of the developing embryo. The individual variations that are obvious even in the classical trisomy syndromes may be due to genetic effects from each individual's unique genetic background. In the deletion syndromes, one may speculate that the great variation among affected individuals with an apparently very similar loss of chromosomal material may be related to the exposed recessive genes on the homologous unaffected chromosome.

To the physician, the presence of the stigmata we have discussed indicates the necessity for an intensive familial and genetic investigation and a search for other possibly related abnormalities. The funny looking facies often is an indicator of some familial disorder. Similarly, the history of several spontaneous abortions may be an indicator of an inapparent (balanced) chromosome translocation in one of the parents. Many of the zygotes produced by a sperm or ovum carrying a translocation chromosome represent nonviable constitutions and will be lost as abortions. Thus, two or more abortions or stillbirths may reflect such a carrier state, and cytogenetic investigations of these high-risk parents should be made.

The possible involvement of more than one genetic factor, as well as possible environmental agents, is frequently demonstrable in a carefully taken family history. The family of the child with Cornelia de Lange syndrome (Fig. 7-19) was marked with several cases of birth defects, such as cleft palate, clubfoot, and syndactly. These sporadic and apparently unrelated defects may represent manifestations of the defective complex of genes responsible for the affected child with the full-blown syndrome. Again, a good physical examination is vital for accurate diagnosis, and a careful family history is equally important for family counseling.

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Chapter 8

The sex chromosome abnormalities

The differences between males and females generally are quite obvious, notwithstanding the confusing haircuts and attire usually in vogue with adolescents of both sexes. Sex has been assigned rather arbitrarily and promptly for most individuals on arrival in the hospital delivery room, according to the outward appearance of the genitalia. The male phenotype is represented by the presence of penis and scrotum; that of the female by her own distinctive external genitalia. Occasionally, the outward appearance of the genitalia may not be obviously either male or female. The phenotype is then ambiguous, and, often tragically, so might be the sex identification and sex role established later on in the individual's life. There are other "intersex" conditions in which the infants may appear sexually normal at birth but in whom development of the gonads is grossly abnormal. Many sex anomalies are genetically determined, and ever growing numbers are now known to be caused by chromosomal aberrations. About one in every 200 newborn infants has a sex chromosome abnormality. Our understanding of the mechanisms of normal and abnormal sex determination and differentiation, together with our use of the newer techniques for cytologic diagnosis of the genetic sex of individuals, makes it possible now for many persons with sex abnormalities to have an opportunity for a reasonably normal life.

SEX DETERMINATION: ROLE OF THE X AND Y CHROMOSOMES

The Y chromosome is necessary for male development, and a double dose of the female determining factors on the X chromosome is necessary for proper development of the female gonads. The sex determination of the individual, in genetic terms, is decided at fertilization. If the sperm carries an X chromosme, a female will be produced; if the sperm contains a Y chromosome, fertilization of the X-containing ovum will produce an XY or male offspring. The factors on the Y chromosomes that eventually promote a masculine phenotype remain somewhat puzzling. Although the male-determining factors are apparently DNA molecules very similar to the classical Mendelian genes, they differ in some respects, such as an absence of dosage effect. Although there is a great variation among

individual males in regard to the size of the Y chromosome, there does not seem to be any increase in masculinity, or virility, in males with large Y's. Conversely there is no lack of masculinity in those males with Y chromosomes on the smaller side. Comparably, the presence of an extra Y chromosome (as in XYY or XXYY individuals) does not bring with it any increased tendency toward maleness.

At any rate, the presence of a Y chromosome furnishes some sort of impetus for the primitive and sexually indifferent gonad to become a testis, and for the embryo ultimately to develop into a male. This differentiation of the sex organs occurs during the second month of embryonic life. On the other hand, if the chromosomal constitution of the embryo is XX, the primitive gonads will develop into ovaries, and the individual will be female. We have evidence that similar female-determining genes are located on the X chromosome. Sex chromatin studies of a group of females with a short stature and other congenital defects (originally described by Turner in 1938), however, showed that females also could be female *simply* because they do not have a Y chromosome. These females had only one X chromosome, with an XO sex chromosome complement. Among these females, even though two X chromosomes are obviously not necessary for female development, the loss of one of the X chromosomes causes improper development of the ovary, along with other somatic defects.

ERRORS IN SEX DEVELOPMENT

The development of the sex chromatin test made it possible, and easy, to establish whether the newborn with ambiguous or abnormal genitalia was male (XY) or female (XX). The test also made it possible to identify infants with abnormalities involving the X chromosome. Use of chromosomal analysis then led to the clarification of the etiology of several sex aberrations and the discovery of a host of new sex chromosome abnormalities, such as the Turner and Klinefelter syndromes.

TURNER'S SYNDROME (OVARIAN DYSGENESIS)

In the chapter dealing with Down's syndrome, we described the probable mechanisms for the production of an abnormal number of chromosomes, specifically involving the 21 chromosome. Nondisjunction of the sex chromosome may also occur. Nondisjunction in either the sperm or the ovum might lead to abnormal zygotes. For example, both X chromosomes might pass into the polar body during meiosis, while none remain in the ovum. Union of this ovum with an X-bearing sperm would form an XO zygote. Similarly, nondisjunction in the sperm might lead to the absence of a sex chromosome, so that the fertilization of a normal X ovum by this sperm would likewise result in an XO individual.

The ovaries do not develop in the female with an XO complement. Instead, only whitish ridges of tissue are found where the ovaries would be normally situated. These "streak gonads" are made up of a fibrous tissue that is without evidence of the normal primordial or developing ovarian follicles or ova. With a

microscope, one can observe only a few remnants of the undifferentiated primitive mesenephric tissue. The lack of germ cells (gonadal dysgenesis or aplasia) means that the involved individuals will have no menarche, they will not develop any of the secondary sex characteristics except for some scanty pubic and axillary hair, they will not menstruate, and they will be sterile. Using the criteria we discussed earlier in this chapter, however, these individuals are female. The development of the internal genital tract and the external genitalia is essentially

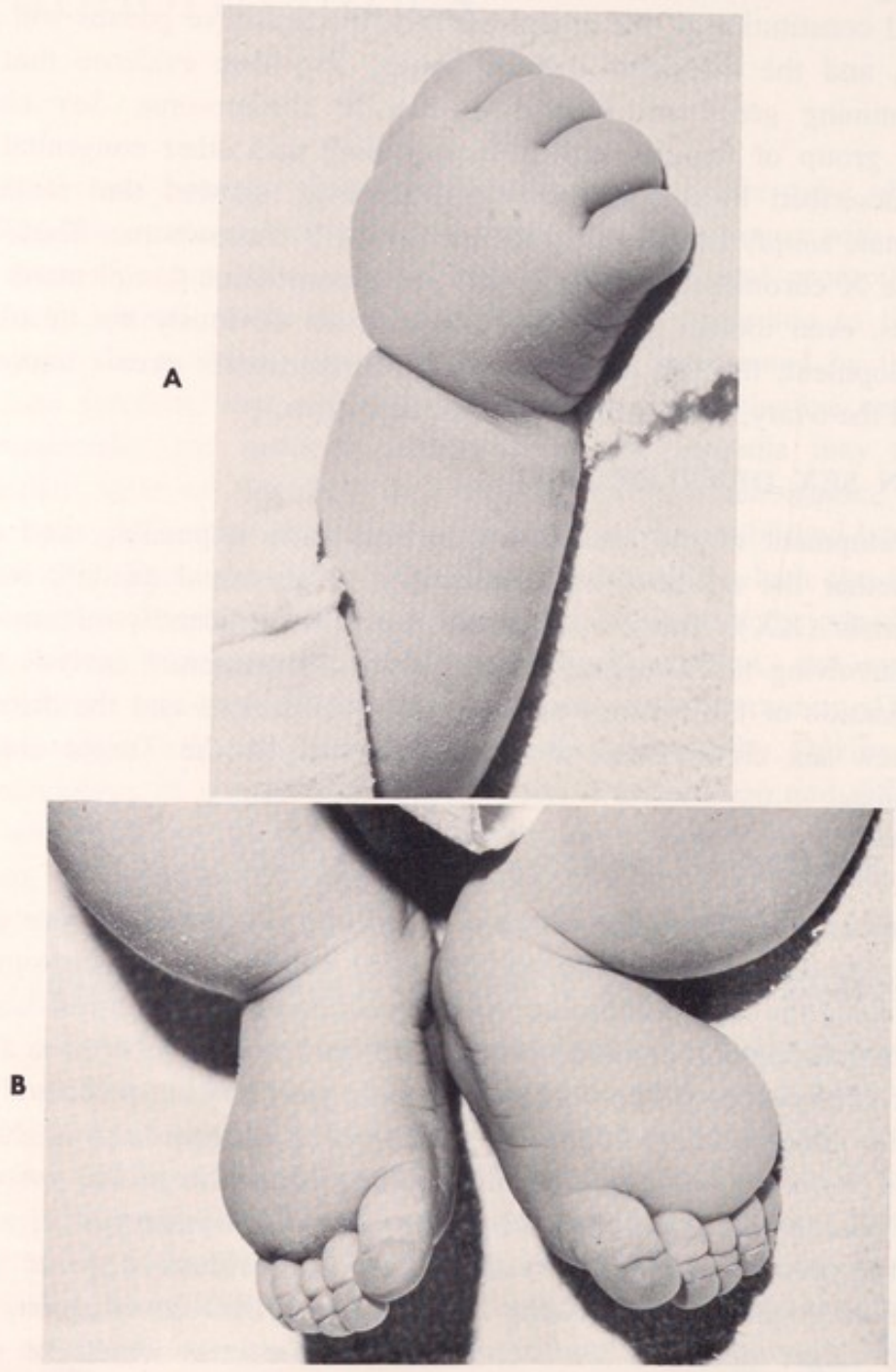


Fig. 8-1. Puffy, edematous hands, **A,** and feet, **B,** are suggestive of Turner's syndrome in the newborn.

female. The external genitalia, however, remain juvenile in appearance even after puberty. The clitoris remains small, and the labia are flat. Also, the fallopian tubes and uterus remain small and immature.

Diagnosis in infancy

It is estimated that about one in 3,000 or so newborn females have Turner's syndrome (XO). In fact, this number probably represents only a fraction of the XO zygotes formed. Studies of abortion tissues indicate that 95% of these XO embryos are aborted. The loss of an X chromosome is obviously often a lethal affair. Indeed, most of the infants who do survive generally have several congenital defects. The infants may show no abnormalities at birth, but frequently there are suggestive findings that could prompt the pediatrician to do the sex chromatin test. The infant with Turner's syndrome will often be in the "low birth weight for gestational age" group. The infant is often born with marked edema of the hands and feet, as illustrated in Fig. 8-1. The edema may persist up to several months of life, but then, as a rule, it gradually disappears spontaneously.

The newborn infant with Turner's syndrome sometimes demonstrates a low hairline and markedly loose and redundant skin folds of the neck (Fig. 8-2). Other anomalies are associated with the syndrome. Heart disease, specifically

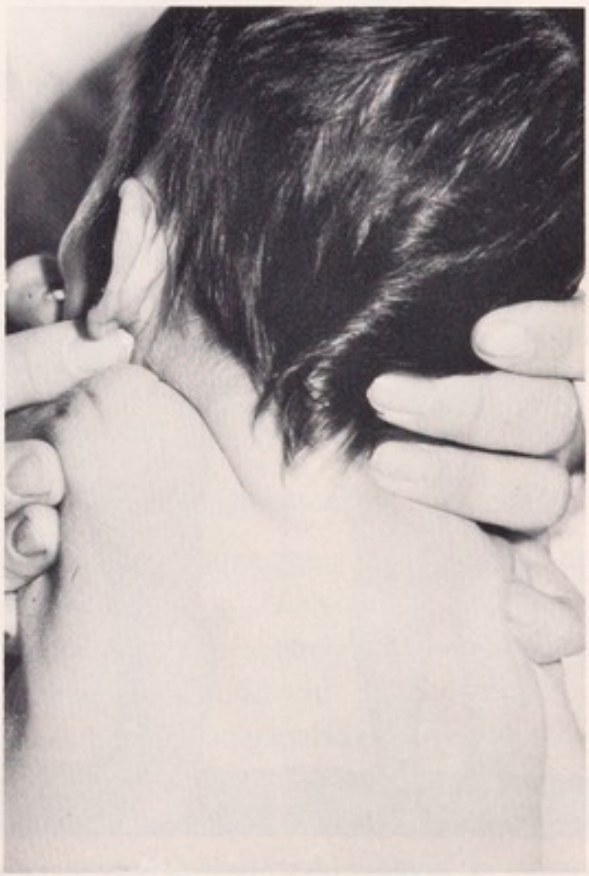


Fig. 8-2. Skin folds and low hairline are associated with Turner's syndrome in infancy.

coarctation of the aorta, is a very common finding. The chest is often shieldlike, with widely spaced nipples. There may be numerous pigmented nevi. Deformities of the hands and feet, such as webbing of the digits, hypoplastic nails, and markedly shortened fourth fingers (due to hypoplastic metacarpal bones) are common. The pediatrician also should be on the alert for other defects, such as deafness and congenital abnormalities of the kidneys, that may not be so obvious on physical examination in the newborn nursery. Dermal patterns may be of some help in early diagnosis. Transverse palmar creases (simian lines) are common. In a good number of individuals the axial triradius is distal in location, and the thumb prints may show ulnar loop patterns instead of the normally expected whorl patterns.

Growth and development

Failure of normal growth and development will sometimes bring the girl with Turner's syndrome to the attention of a doctor. The individual with Turner's syn-

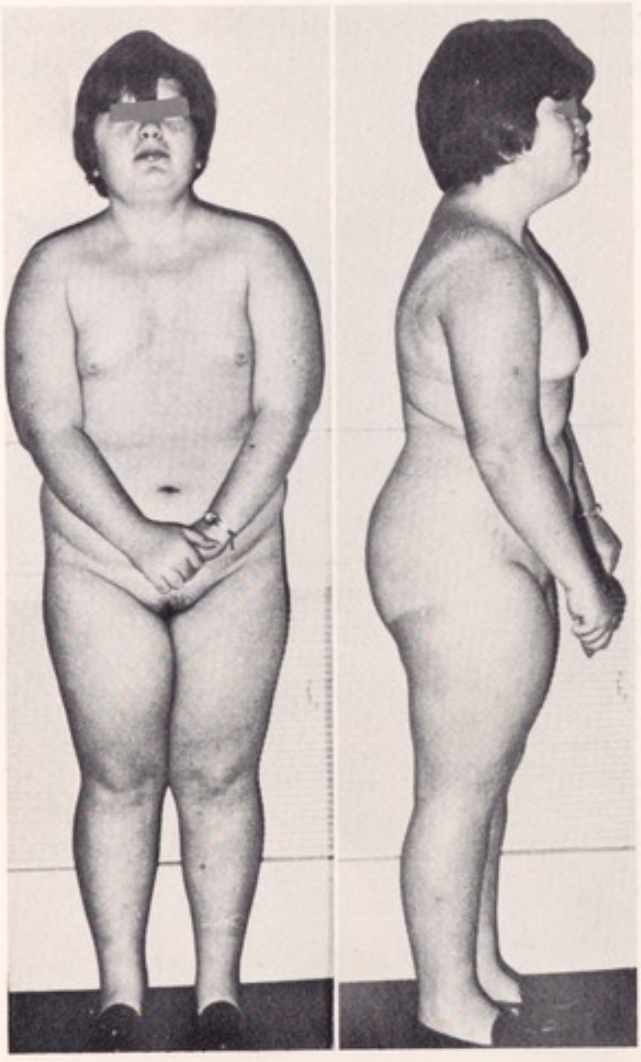


Fig. 8-3. Shortness of stature, a webbed neck, lack of secondary sexual development, and amenorrhea are the chief signs of Turner's syndrome during adolescence.

drome will rarely attain a height of five feet. Most often, however, help is sought only when the common changes of puberty do not appear and there is a failure to begin menstruation. The 16-year-old girl shown in Fig. 8-3 demonstrates the features of the syndrome at this time. She has the webbed neck (pterygium colli) and low hairline; she also demonstrates the lack of breast development and of pubic hair. Her external genitalia were juvenile in appearance. When we saw her, she was 58 inches in height, and we could safely predict that she would remain short. In fact, dwarfism is the usual condition found among children with Turner's syndrome. Although epiphyseal closure may be delayed and growth continued at a slow pace until 20 or 21 years of age, growth may abruptly cease at the time of puberty.

The personality of the adult with Turner's syndrome is frequently characterized as childlike. She is likely to be timid, unusually dependent, and lacking in drive and initiative. Apathy and unresponsiveness in social behavior also characterize her sexual behavior. Although some women with Turner's syndrome may have normal erotic functioning, including orgasm during intercourse, the tendency is for most women to have lower levels of erotic functioning. Evidence of immaturity and related forms of psychopathology may be as much related to the psychosocial problems of dwarfed stature and hormonal problems as to the missing genetic material on the X chromosome.

Intellectual deficits have been found to be linked with Turner's syndrome, but the nature of these deficits still constitutes a problem. Although mental retardation has been frequently cited as an associated anomaly in this syndrome, recent evidence does not bear out this early impression gained from evaluating patients in institutions. Intelligence quotients tend to average in the normal range of intellectual ability.

There is, however, some evidence that a specific deficit involving space-form perception is associated with the loss of the X chromosome. Many children and adults with Turner's syndrome have been found to have some difficulty in recognizing or reproducing geometric figures, drawing, constructing puzzles, and analyzing intricate designs. Learning handicaps associated with this type of perceptual problem are likely to involve reading and writing proficiency, and for this reason special education should be considered as part of the therapeutic regimen.

Chromosome findings in Turner's syndrome

A majority of patients with Turner's syndrome have an XO karyotype (45 chromosomes), as shown in Fig. 8-4. The X chromosome that is lost may be either paternal or maternal in origin. The scanty evidence available indicates that the average age of the mother having a child with Turner's syndrome is not much higher than the average age of mothers in the general population. Therefore, unlike Down's syndrome, Turner's syndrome does not appear to be maternal-age–dependent. There is better evidence for nondisjunction errors on the paternal side. A sex-linked recessive disorder, red-green color blindness, is present with the same frequency (about 8%) in females with Turner's syndrome as in normal males. There-

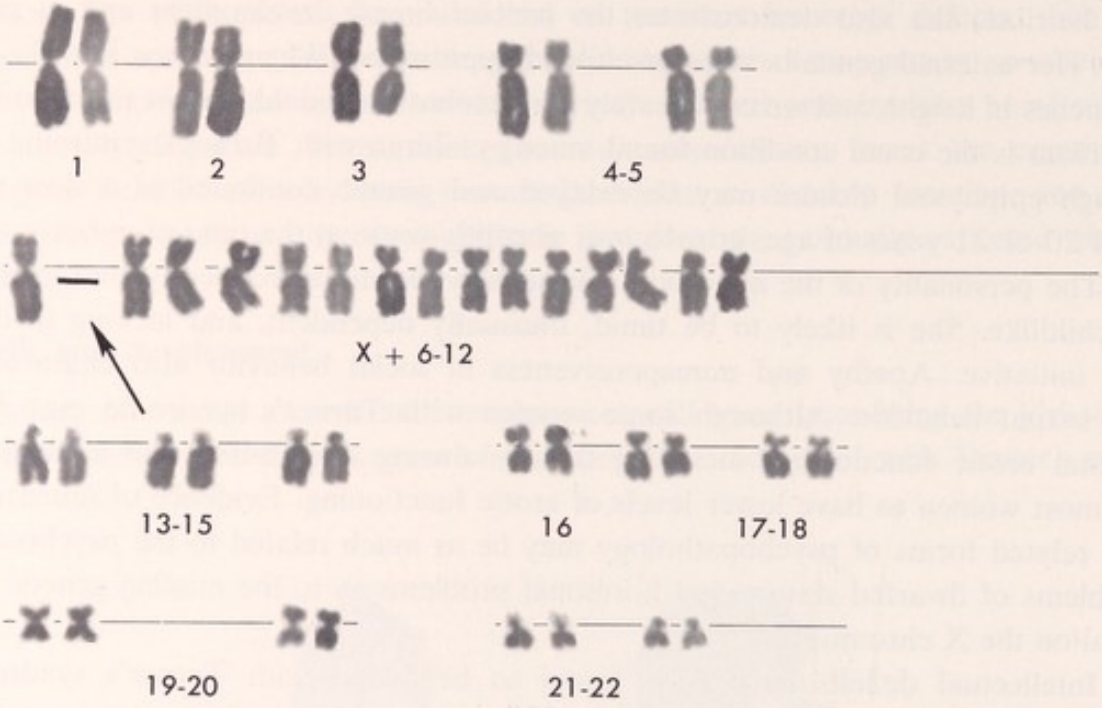


Fig. 8-4. Karyotype in Turner's syndrome indicating the missing X chromosome, arrow, and 45 total chromosome number.

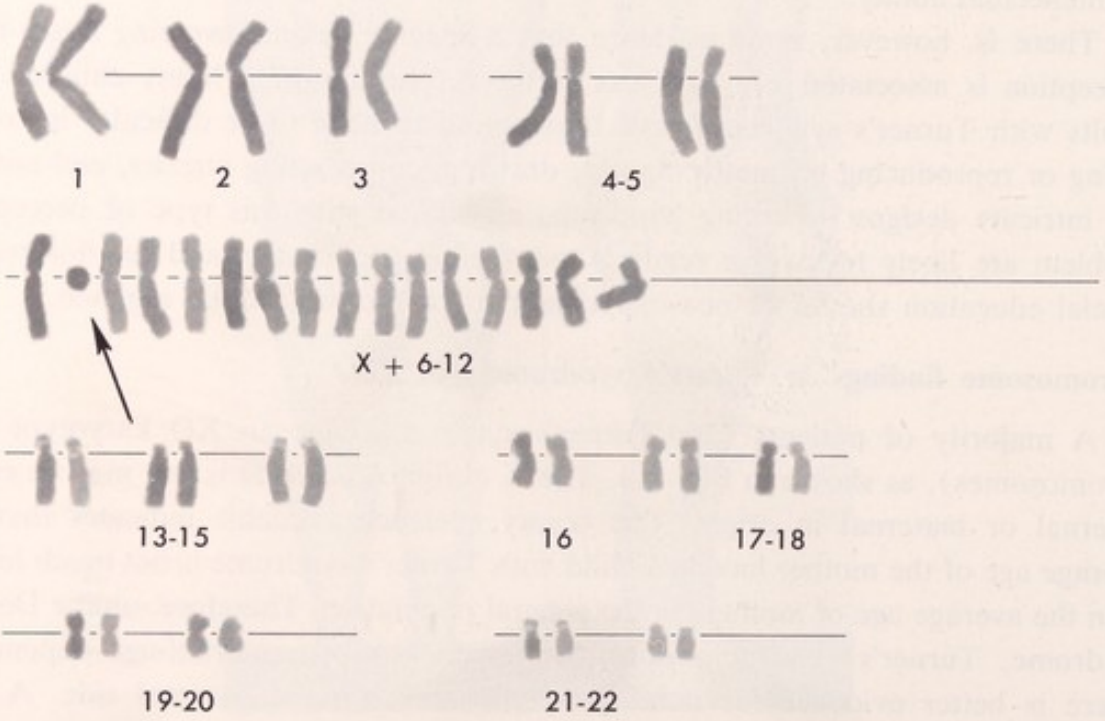


Fig. 8-5. Karyotype showing a ring chromosome, arrow, which replaces the normal X chromosome.

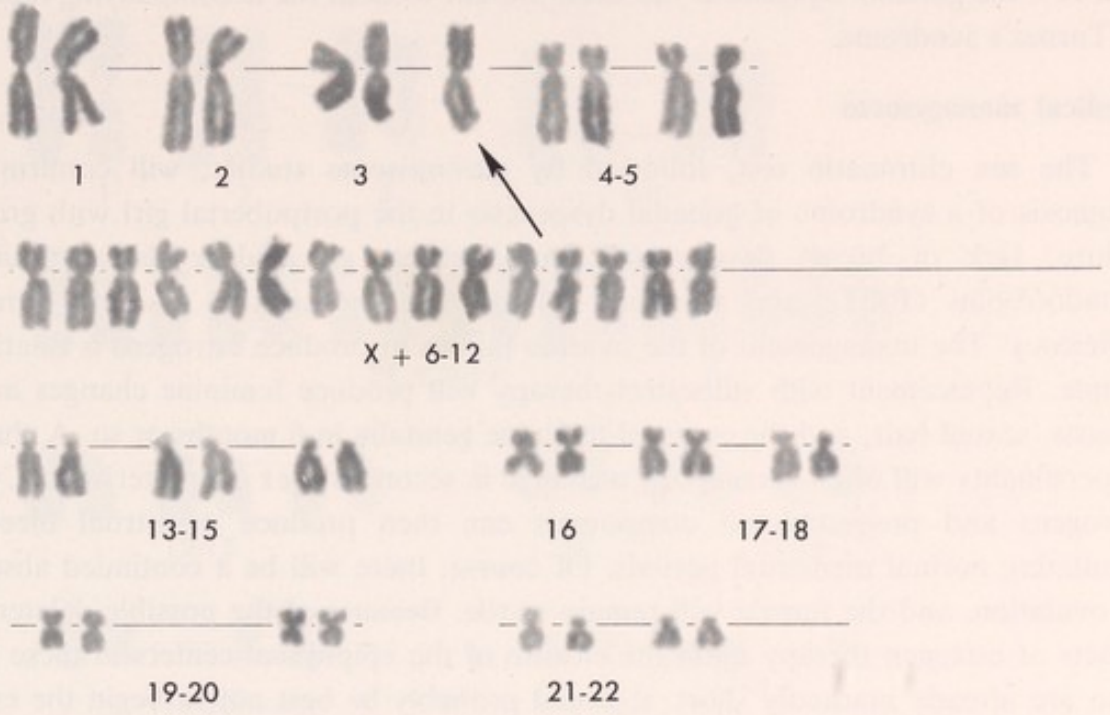


Fig. 8-6. Karyotype with an arrow indicating an isochromosome X, made up of both long arms of the X chromosome that replaces a normal X chromosome.

fore, one may safely speculate that the X chromosome bearing the mutant gene came from the mother, while the male gamete (sperm) must have lost the sex chromosome in these individuals.

The next most common chromosome finding in Turner's syndrome is XO/XX mosaicism. Our own experience indicates that about one third of the patients studied are of the mosaic type. It is believed that most cases of mosaicism are due to an abnormal disjunction that takes place at one of the early mitotic divisions of the zygote, instead of during meiosis in the original gametes. Most of these mosaic females show the complete Turner's syndrome phenotype, including gonadal dysgenesis—but the occasional fertile Turner female reported may certainly represent a mosaic, in which there are probably enough XX cells present early in embryonic life to stimulate normal ovarian development. The sex chromatin pattern in the mosaic Turner is generally positive; but the percentage of Barr bodies, which may be low, is in the range of about 10% to 20%.

Occasionally, in Turner's syndrome, the entire X chromosome is not lost. Instead, a deletion of the upper (or short) arms of the X chromosome may occur, as, for example, during ring formation (Fig. 8-5). Such a deletion results in the full Turner's phenotype. Similarly, presence of an isochromosome made up of the long arms of the X chromosome also will result in Turner's syndrome (Fig. 8-6). It would seem that the factors causing the anomalies associated with Turner's syndrome—short stature, webbed neck, etc.—are associated with loss of the upper arms of the X chromosome. In those females (isochromosome short

arm X), the gonadal dysgenesis has been present without the accompanying features of Turner's syndrome.

Medical management

The sex chromatin test, followed by chromosome studies, will confirm the diagnosis of a syndrome of gonadal dysgenesis in the postpubertal girl with growth failure, lack of breast development, amenorrhea, elevated levels of pituitary gonadotropins (FSH), and a vaginal cell smear demonstrating a severe estrogen deficiency. The management of the ovarian failure to produce estrogens is relatively simple. Replacement with stilbestrol therapy will produce feminine changes in the breasts, sexual hair, and the external feminine genitalia in 6 months or so. A change in personality will often accompany a change in secondary sex characteristics. Cyclic estrogens and progestational compounds can then produce menstrual bleeding simulating normal menstrual periods. Of course, there will be a continued absence of ovulation, and the female will remain sterile. Because of the possible deleterious effects of estrogen therapy upon the closure of the epiphyseal centers in these girls who are already markedly short, it would probably be best not to begin the estrogen therapy until the age of 13 or 14.

KLINEFELTER'S SYNDROME

Klinefelter's syndrome is more common than the Turner anomaly and probably represents the most common sex chromosome abnormality. It was also one of the first defects of any kind to be related to a chromosomal anomaly. The frequency of this syndrome is in the range of one in 400 live male births. This syndrome, represented by sterility, atrophic testes, and elevated urinary gonadotropins, was described in males some 15 years before its etiologic relationship to an abnormal sex-chromosome complement was identified. Males with Klinefelter's anomaly are sex-chromatin positive, indicating the presence of two X chromosomes. The sex chromosome makeup does prove to be XXY, with a total chromosome number of 47 (Fig. 8-7).

Again, our best explanation for formation of the XXY individual is that there is a failure of proper disjunction in one of the meiotic divisions. Since, on statistical grounds, there is apparently some influence of maternal age in Klinefelter's syndrome, the nondisjunction accident may primarily be in the gamete contributed by the mother. Evidently the presence of the Y chromosome ensures the development of a male phenotype in spite of the presence of an extra X chromosome. The male that is produced, however, is sterile and generally has many other problems after puberty.

Prior to puberty, the diagnosis of Klinefelter's syndrome would be most difficult on clinical grounds alone. One of the only clues that may be present is that of mental retardation, which is common among persons with this disease. In the greatest number of instances, early detection of Klinefelter's syndrome results from a sex-chromatin survey of the newborn, or, most frequently, a survey of an institution for

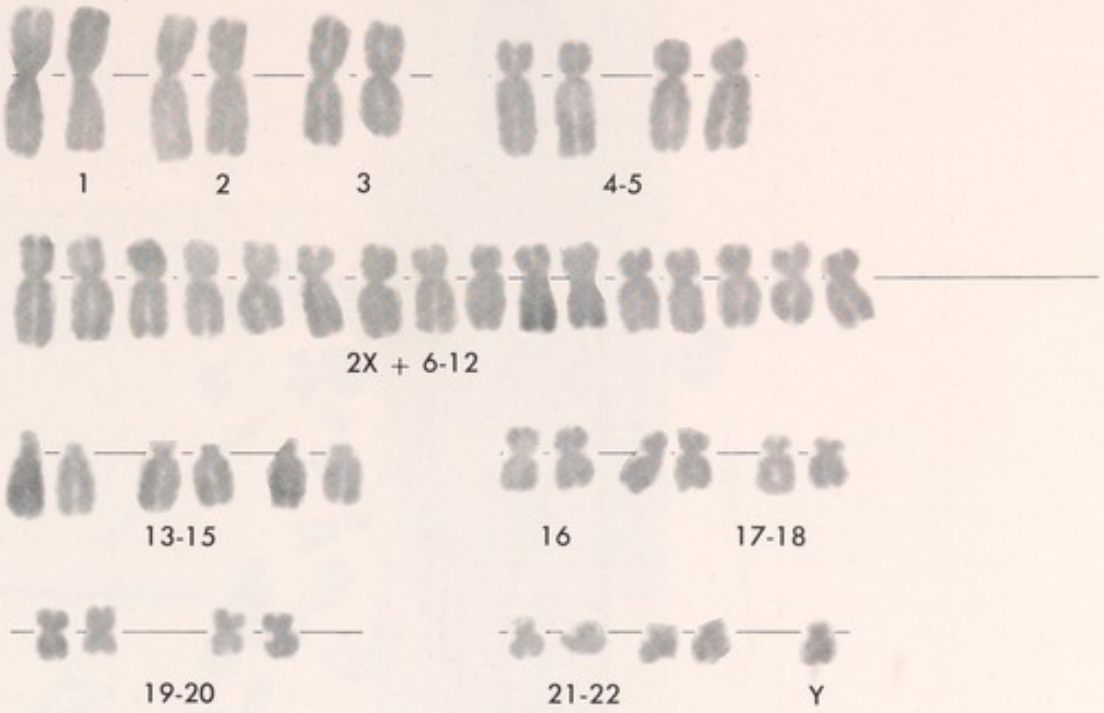


Fig. 8-7. Karyotype of an individual with Klinefelter's syndrome. This karyotype shows the XXY (47 chromosome number) pattern.

mental retardates. The association of mental retardation with the XXY syndrome is real. It is estimated that perhaps one in fifty of the institutionalized male retardates is XXY (or about ten times the number of such individuals in the male population).

After puberty the physical appearance may give some hint of the XXY constitution. The individuals may be tall and eunuchoid; enlargement of the breasts (gynecomastia) may be present; the pubic hair may be sparse, with a female escutcheon; facial hair may be scanty. There is great variability even in these findings, however, so that physical examination might reveal only the small, firm testes characteristic of the syndrome. The urine will also show a marked increase in pituitary gonadotropins. As in Turner's syndrome, the failure of the target organs (the gonads) to respond causes a block in the pituitary gland feedback mechanisms, so that there is an increase in its own output of pituitary hormones.

Spermatogenesis is absent on examination of the testes. Microscopic sections from biopsy reveal the degeneration of the seminiferous tubules and other atrophic changes in the testes.

Despite the bias introduced by the samples used in several studies on Klinefelter's syndrome, the tendency is for such persons to be vulnerable to a range of psychological dysfunctions, including mental deficiency. Homosexuality, sexual psychopathology, psychopathic criminality, and schizophrenia represent some of these dysfunctions. Specific learning disabilities such as dyslexia and speech disorders are also found.

It is obivous that sexual behavior will be affected by this syndrome, and, indeed, it is rare to find a moderate to strong sexual drive among affected adults. The

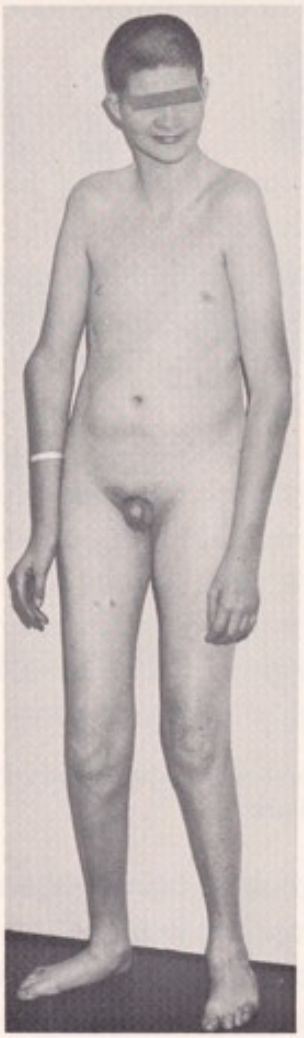


Fig. 8-8. A 19-year-old profoundly retarded individual with XXXXY sex chromosome constitution.

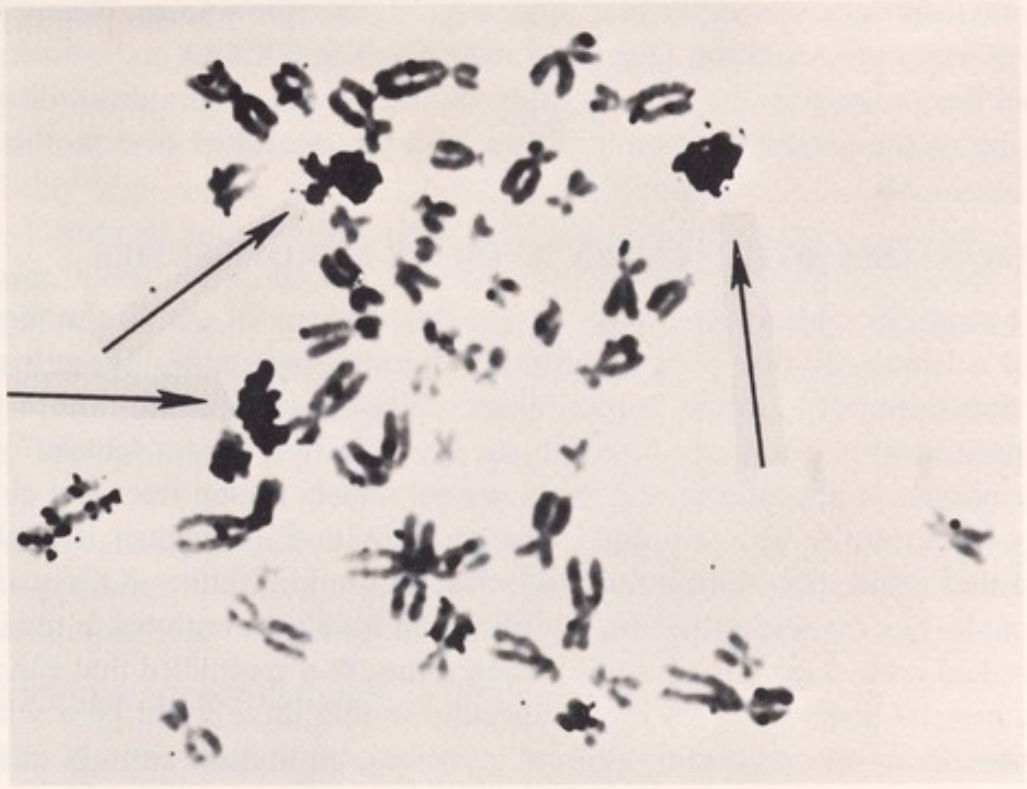
sexual urge is usually weak, and erotic activities are infrequent. Total impotence, however, is unusual, as is a total absence of interest in sexual activities.

Medical management

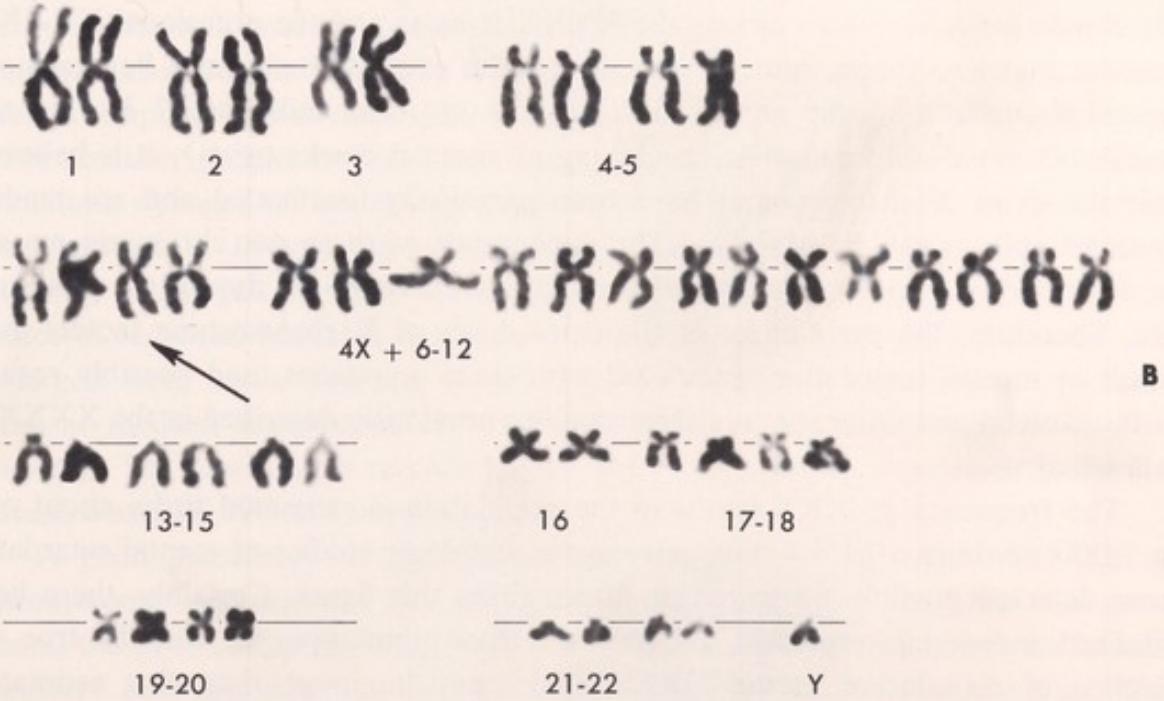
The penis is generally of normal size. Sexual functions, such as erections, ejaculation, and intercourse, are potentially normal. As we mentioned before, the libido and sexual drive are, however, diminished in these individuals. Medical management consists of the use of testosterone, which will certainly lead to a more masculine body build, normal hair distribution, and, frequently, an increased sexual drive and potency.

THE XXXXY SYNDROME

Individuals with more than one extra X chromosome have also been described. The XXXY male (probably due to an error in cell division in *both* stages of the meiotic process in one of the gametes) has a very similar clinical picture to the



A



B

Fig. 8-9. A, Metaphase figure with tritium labeling demonstrating three "hot X" chromosomes, arrows, in the patient's cells. **B,** Karyotype of XXXXY individual.

XXY individual. A further extra X chromosome (the XXXXY male), however, produces associated congenital defects, so that XXXXY males probably should not be considered as just variants of the Klinefelter syndrome. Mental retardation in the XXXXY male is generally much more profound than in the XXY and XXXY syndrome, and, moreover, there are skeletal anomalies. These anomalies characteristically are radioulnar synostosis of the elbow joint, "funny looking facies," and hypogenitalism (Figs. 8-8 and 8-9). The XXXXY individual, however, does demonstrate the importance of the Y chromosome in sex determinations, for in spite of the extra three chromosomes, and the associated defects, these individuals are male.

ABNORMALITIES WITH "EXTRA X OR Y" CHROMOSOMES

In *Drosophilia melanogaster* (the vinegar fly), trisomy of the X chromosome results in a female fly that is morphologically normal, but sterile. These triple X vinegar flies have been termed "super females." The human female with a triple X sex constitution is better off. Although she is not really a "super female," she is perfectly normal in appearance and has a normal female genital tract and gonads. In fact, she is fertile, with a normal menstrual cycle. Even though it might be expected that about half of these females' offspring would be either XXY males or XXX females like the mother, all the newborns that have been reported in the literature have had normal sex chromosome complements. It is speculated that either the XX ova may be inviable, which seems unlikely, or that there might be a selective segregation during the disjunction process in meiosis, so that the extra X chromosome always migrates to the polar body.

Mental retardation is apparently increased in these individuals. The frequency of retardation is very high among the XXXX females and the occasional XXXXX females that have been studied. Why do not the extra chromosomes have a more deleterious effect on the sexual development of these individuals? During the weeks of sexual differentiation (beginning at about 6 weeks or so), it is believed that the extra X chromosomes have been genetically inactivated and are readily demonstrable as the Barr bodies. The appearance of these sex chromatin masses in the embryos is not noted until the eighteenth to twentieth day of the embryo's life. Therefore, the early effect of the extra doses of X chromosome factors may result in mental retardation associated with these anomalies, and possibly results in the skeletal and other somatic abnormalities previously described in the XXXXY individual.

The frequency of XXX births in the population is estimated to be about one in 1,000 newborn (0.1%), but, once again, cytologic studies of mental retardates have detected possibly up to ten or fifteen times this figure. Certainly, these hospitalized individuals represent a highly selective population, so that the true incidence of retardation in the XXX female may be lower than that estimated from these types of studies. Again, although there is superficially much higher incidence of the XXX anomaly than, for example, the XO Turner's syndrome, we

must remember that there is a high incidence of fetal wastage of embryos with the XO anomaly. Consequently, the true incidence of these multiple sex chromosome anomalies may be similar.

The Y chromosome apparently does not contain much genetic information. Except for the testis-forming factors, there seems to be only a mutant gene causing "hairy ears" among some Indian families. An interesting finding has been made in males with an XYY karyotype. We have noted previously that there does not seem to be any additive effects of "maleness" in men with the XYY or XXYY karyotypes. The incidence of males with XYY karyotypes, however, has been remarkably high among individuals hospitalized because of subnormal intelligence and violent and antisocial behavior. The majority of these men are also tall—6 feet or over. Certainly, since routine buccal chromatin preparations cannot detect abnormalities of the Y chromosome, surveys of institutions will produce highly selected populations (as we have often emphasized). More studies will have to be made before we can conclude that a double dose of the Y chromosome can produce the behavioral changes that have been associated with the YY make-up.

Although abnormalities in the number of either X or Y chromosomes do cause problems involving intellect and fertility of affected individuals, true "intersex conditions" are more likely to be caused by cell mosaicism.

"INTERSEX CONDITIONS"

The intersex individual may have ambiguous or confusing genitalia, or may have characteristics of both sexes. It is for the intersex conditions, especially, that a diagnosis should be made as early as possible. The assignment of sex may not necessarily be derived from the chromatin sex pattern or the chromosome analyses. The external genitalia, the hormonal status of the patient, and sex of rearing may be of greater import in the final determination of the sex. The decisions about sex determination should be made early enough in infancy to avoid the necessarily traumatic changes of sex typing made in later life. For example, let us consider the case of a 15-year-old phenotypic female brought to our clinic. She, at puberty, had begun to show a deepening voice, facial hair, and all the other evidence of testicular hormone production. Although the clitoris had been noted to be enlarged from birth, and the mother had felt something was wrong, there had been no medical investigation undertaken until the embarrassing events occurred at puberty. The family now considered the girl to be a freak. Chromosome analysis revealed an XY/XO sex constitution.

A good percentage of the intersex individuals have the mosaic XO/XY sex chromosome constitution. The Olympic games committee has had, in recent years, the problem of deciding the sex of some of the better-built women hammer throwers and javelin throwers who come from behind the Iron Curtain. These individuals have a negative sex chromatin pattern. The great variation in the phenotypes of the external genitalia in the XY/XO mosaic individuals makes such

confusions quite possible. Such persons may be phenotypic males or females, apparently depending upon what percentage of the cells contain a Y chromosome. They almost always have ambiguous genitalia, they may have only rudimentary gonads, and for the most part they are sterile.

The girl with the virilizing changes at puberty, mentioned previously, proved to have a testis on one side of the abdomen. She also had a "streak" ovary, similar to that found in Turner's syndrome, on the other side of the abdomen. She was thus a true *hermaphrodite*. The clitoris was surgically amputated. Removal of the testes in a second operation made her in time an attractive young lady once again. It was emphasized to her parents that she was very much a female, certainly not a freak. Of course, on many occasions the need for cosmetic changes in external genitalia and appearance cannot be met by corrective surgery; likewise, as we will discuss later, other problems that have arisen may not be so readily soluble.

True hermaphrodites have both ovarian and testicular tissue, either as separate gonads on either side of the abdomen or as a single organ, an *ovotestis*. The external genitalia may appear to be either male or female. The internal genital tract also varies in its sexual identity. These sex chromatin patterns may be negative or positive (frequently the latter), and chromosomal analyses may reveal an XX, XY, or a host of mosaic patterns, such as the XO/XY pattern. Although the majority of these individuals are genetically female (XX), the genitalia usually are primarily masculine-appearing. It is interesting that even in the true hermaphrodite with an XX sex chromosome pattern, testicular tissue and some male characteristics can occur seemingly without the presence of a Y chromosome. Mosaicism, possibly in the gonadal tissue alone, of course, may be undetected through the use of present techniques.

GENETICALLY DETERMINED SEX ABNORMALITIES

We stated earlier that there are some genetic causes of intersex conditions. These are unrelated to *gross* chromosomal abnormalities. One heritable defect may be detected in the newborn. Congenital adrenal hyperplasia is caused by a genetic mutation involving the production of adrenocorticoid hormones. The lack of an enzyme (or possibly several related enzymes) causes a block in production of the normal adrenal hormones and also results in an increase in masculinizing hormones. In a male infant the changes may not be noticeable, although precocious puberty appears in late childhood. In a female there may be such marked masculine development of the external genitalia that they are, for all practical purposes, male in appearance, with scrotal-like fusion of the labia and penile urethra. These females, of course, have *no testes;* the internal genitalia remains female in morphology. It is especially vital that the diagnosis of this disorder be made shortly after birth. A sex chromatin test is important. Frequently, of course, these infants develop the full-blown symptomatology of Addison's disease because of the adrenal hyperplasia, and they have great difficulty in the first few days of life. A familial history is often at hand, since adrenal hyperplasia is a recessive abnormality. Many of the bearded ladies of the circus probably had this abnormality.

TESTICULAR FEMINIZATION

The development of the normal male reproductive tract depends upon the action of the masculinizing hormones produced by the testis. This action begins about the third month of the embryo's life. Deficiency of these normal testicular hormones might well produce abnormal development, or even an absence of the male organs. Testicular feminization is another inherited disorder that causes male pseudohermaphroditism. The patient with testicular feminization is female in external appearance, and in fact is frequently tall and beautiful. Very often the patient with testicular feminization is married. She goes to the doctor only because of amenorrhea. We have also seen an 8-year-old girl who was hospitalized because of bilateral hernias, which at operation were discovered to be testes. Most often, however, the testes in these individuals are located in the abdominal cavity. The clitoris may be somewhat enlarged, and a vagina is generally present. Inspection reveals, however, that the vagina has a blind pouch and the genital tract is male. Despite the fact that these individuals are genetically male, they almost always are reared as females. The inheritance pattern is not clear, but it does seem to be an autosomal-dominant one, and it is expressed only in XY individuals. It would seem, therefore, that individuals with testicular feminization syndrome are inheriting the abnormal gene from the mother. The basic cause of the abnormality is the secretion by the testes of estrogens instead of androgens, so that the testes really have a feminizing, instead of a masculinizing, effect.

COUNSELING CONSIDERATIONS

The diagnosis of the sex chromosome abnormalities, if ideally made when a child is still an infant, should present few complications for counseling. At that time, the counselor could best advise the parents about the sexual identity that would be most appropriate for the child. Dependent on the sexual abnormality and the parents' and physicians' decision, medical management procedures could be considered that would, then or later, establish the genital and other physical characteristics of the chosen sex. In addition, the physician could advise the parents about establishing life expectations that could be realistically inculcated by them in the child. For example, the detection of an intersex condition at an early age would allow the parents, with medical consideration, to establish the sex of the child and to rear the child accordingly. Furthermore, the parents could induce appropriate mating or childbearing expectations in the developing child. When the child becomes an adult, considerations for marriage or family should already be firmly established on realistic expectations. In this fashion, our diagnosis of sex abnormalities during the patient's infancy should help the patient to avoid the ambiguities of sexual identity and expectations of an adult's life.

Unfortunately, the usual delay in diagnosing sex chromosome abnormalities brings into play a host of difficult questions that plague, and will continue to plague, the counselor and the family. A child reared as a boy for fourteen years is not easily changed, on genetic grounds, to a girl—and one questions whether such a change should be made. Genetic factors notwithstanding, the psychosexual con-

ditions in a child's history more than override whatever our medical facts tell us. Also one questions whether the diagnostic information should be passed on to the patient, and, if it should, when. Should, for example, the adult woman with Turner's syndrome or testicular feminization be told about the abnormality? If we have the diagnostic information available, should we tell it to a girl after puberty, prior to her marriage, after her marriage, or not at all? The same kinds of questions can be raised about counseling male patients about their sex abnormalities.

We recognize that there are no pat answers to some of these questions. What does seem clear is that decisions to change a patient's sexual identity should be made with the age of the patient in mind. Sexual differentiation is influenced early in life by language, dress, and exposure to experiences related to the assigned sex. Even in the first one or two years of life boys are treated differently from girls. We expect different behaviors from each sex, and we also prohibit different behaviors. By the time a child reaches puberty, he or she has had several years of experience related to a particular gender. Medical management, through hormone treatments or surgery, may change masculine or feminine aspects of the patient, but we cannot undo this history. In fact, we generally consider it the better course to let the assigned sex stand. Then we can use whatever medical and psychologic tools we have to support the continued assimilation of all that a particular sexual identity entails.

The more delicate question of what to tell the postpubertal child or the adult with a sexual abnormality entails more than what sexual identity has been established for the patient over time. This question brings into play the expectations that the patient has for a life as an adult. The patient's expectations, derived from parents and peers (as well as the movies, magazines, etc.), are, in our society, usually centered on marriage and childbearing. Even in this age of concern about population control, the biases built into our social customs, tax laws, and insurance rates usually do not favor unmarried persons or childless couples. Although the emphasis on normal expectations may vary, depending on the family and the subculture, getting married and having children are held up as appropriate actions to be emulated by everyone. Persons with sex chromosome abnormalities, even those diagnosed at an early age, do not escape from this emphasis.

As we stated earlier, we can offset the emphasis on marriage and childbearing by making the diagnosis of the sex abnormality as early as possible. The child can learn that to be unmarried, or to be married but childless, is not the same as accepting a lower station in life. Such a child, upon reaching the age when it is appropriate to be told something explicit about the abnormality, is prepared to receive realistic information.

When the diagnosis is made later in the patient's life, particularly when the patient is an adult, the patient is less prepared to accept a different set of expectations about marriage and family. For obvious reasons, neither the family nor the patient has thought about setting up different goals. In these instances the counselor should be especially attentive to the personal touch in his relation with the

patient and the family. Counseling rapport is strongly needed. It can come, or perhaps should come, from a personal family physician. Also at these times the counselor should be most prepared to utilize whatever help is available from the clergy, guidance, family or marriage counselors, and appropriate members of the medical specialties.

We can classify counseling the postpubertal patient into two general areas of consideration: the kinds of information we give to patients prior to marriage and the kinds of information we give to patients after marriage.

The patient counseled prior to marriage often has been diagnosed because of abnormalities noticed at the time of puberty, or because of a routine premarital examination. In the former case, counseling is usually directed toward the parents, who, it is hoped, will explain the pertinent medical information at the appropriate time. Young adolescents usually indicate an interest in marriage and family, but these interests are somewhat vague and abstract. The immediate concern of the adolescent is to look and act like the established sex. Dating is more important than some future goal of marriage. Therefore, the physician's medical management and the parents' explanation of the medical information can center on maintaining the adolescent's sexual identity. It should be recognized, however, that the parents and the physician should be prepared to give the adolescent more information when sexual concerns are voiced or when marriage becomes more imminent.

If the diagnosis of a sex chromosome abnormality is made during a premarital examination, it is imperative that the patient be counseled at once. The patient's parents, a clergyman, or even the spouse-to-be may be involved in the counseling, but the emphasis should be placed on informing the patient. Counseling at this time is important to the patient in terms of his or her goals for marriage. Also, counseling at this time may help to offset the unrealistic expectations of the patient and the future marriage partner for having children.

As we have indicated, some sex abnormalities do not render the patient infertile, but most of them do. When the patient is not fertile but is sexually adequate, marriage is not out of the question, but it is best for the patient to recognize that having children is. This information should be shared with the future marriage partner so that the marriage is embarked upon with realistic expectations by both partners. Sterility does not automatically endanger marriages, but it certainly has led to some divorces. Furthermore, sterility, in one guise or another, is recognized as a legal ground for divorce in better than half of the states. The counselor should be prepared in these situations to advise the patient, or perhaps the to-be-married couple, about adoption and the procedures for adoption. As we have seen in many cases, this information alone will help to offset the negative aspects present for a couple who are contemplating a childless marriage.

The patient diagnosed and counseled after marriage, sometimes after a marriage of many years, demands more individual consideration than any of the other patients mentioned. In some cases, we may see such a patient because a marriage has been childless. Female patients may come to us because of amenorrhea; male

patients may come because of their concerns about a low sex drive. In all of these cases, the counselor should gain as much insight as he can into the marriage relationship: the shared goals of the couple, the marriage pattern of the couple, and the stability of the marriage. Personal rapport with the patient and the spouse is obviously essential, and, for this reason, the ideal counselor is most likely to be the family physician.

With some exceptions, we have found it important to counsel both the patient and the spouse at the same time. The exceptions have usually been made for female patients who, because of their age, their established marriage pattern of being childless, or their image of themselves as "adequate females," are not interested in medical information about sterility. These patients usually are concerned about physical abnormalities that have evoked concern about menopause, cancer, or some other condition. For example, one case we saw involved a military officer's wife who had been diagnosed as having testicular feminization. She had been referred to us because of her concerns about amenorrhea. The patient was 37 years of age and had had a happy, sexually compatible married life for 12 years. Both she and her husband enjoyed a somewhat nomadic existence without children. At their age they neither expected nor wanted any children. In this case, we did not feel the need to counsel the husband at all, and the patient was told only those facts related to her concern. To arm her or her husband with medical facts that would be unimportant for their life, we thought, would produce unnecessary complications.

Other patients have come to us after their abnormalities had been detected by vigilant physicians who were seeing them for other reasons. Again, these patients have demanded utmost consideration in terms of what we knew about their lives and their self-image. Strict adherence to our general rule for honesty has had to be tempered in many of these cases for psychological reasons. Some of these patients, unaware of their abnormalities, have often come to terms with the effects of their abnormalities. Other patients have not even been aware that they were different. Information given to these people is of little use if the medical "insight" produces maladjustment. For example, for many males virility is an important aspect of a masculine self-image. Sterility in males who are not impotent can evoke doubts about an adequate masculine image. If the question of sterility is not pertinent to a marriage or a heterosexual relationship, there is no need to raise that question. We recently saw a case that illustrates this point. A man was referred to our genetic clinic after a physician had observed that he showed physical anomalies indicating a sex chromosome disorder. We found that the man had Klinefelter's syndrome. During our evaluation, we further learned that this man was providing child support to four different women for children of whom he proudly claimed parenthood. Although the man had not been married to any of these women, he believed that his relations with them were such that child support payments were properly imposed, and he gladly paid. We considered that this man's strong masculine self-image, or to use a Spanish term, *machisimo,* was too important to indicate to him that he was sterile.

We recognize that there are many variations in counseling about sex abnormalities. We have treated only aspects of those abnormalities in which the patients have not been mentally retarded, and in which sexual identity, marriage, and having children are the important considerations. Obviously when mental retardation is involved, as is the case in many of the patients with Klinefelter's syndrome or in the patients with XXXXY syndrome, counseling is directed more to the parents' understanding of mental retardation and allied limitations.

We also recognize that we have been arbitrary in classifying the patients to be considered for counseling and in discussing how counseling might be approached. Of all the kinds of genetic disorders mentioned in this book, sex abnormalities produce some of the most subtle, and, therefore, difficult counseling problems. Our discussion, based on our judgment and experience, will probably treat the problems in a manner antithetical to the approaches of some other counselors. Without doubt, other interested parties—clergymen, marriage counselors, psychologists, and lawyers, to mention but a few—can make important contributions to this discussion. Our hope is that all contributions from all sources, whether in agreement or disagreement, will add up to better counseling for the patients and their families.

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Chapter 9

The sex-linked disorders

The sex chromosomes are generally associated with the determination of the individual's sex. With possibly one exception (mentioned at the end of this chapter), the Y chromosome seems to have no function except for inducing masculine sex development. The X chromosome, on the other hand, is known to carry many hereditary factors completely unrelated to ovarian development or sex determination. In fact, the X chromosome probably bears more genes related to important traits than many of the 44 individual autosomes. At the present time there are 75 or so Mendelian genes on the X chromosome. We recognize these genes because of the phenotypic expression through disorders and anomalies caused by mutations. We discussed the nature of genetic changes in Chapter 5.

X chromosome mutations may be fully expressed even if they are recessive. This is unlike the nature of autosomal-recessive conditions, in which the heterozygote does not usually manifest any symptoms or expressions of the disease. Indeed, the vast majority of the so-called X-linked (or sex-linked) disorders of man are recessive disorders. The recessive hemizygotic male with such disorders as hemophilia or color blindness can readily be detected since this individual is obviously affected. This chapter will provide a discussion of sex-linked inheritance, some of the newer concepts concerning the "Lyonization" of the X chromosome, and some considerations related to counseling about sex-linked disorders.

SEX-LINKED INHERITANCE

Sex-linked genes are carried on the X chromosome (again, for a moment, disregarding the possible factors on the Y chromosome). We have shown in the pedigree of the royal family in Chapter 2 the X-linked type of inheritance. The pedigree depicted is similar to that of many thousands of nonregal families afflicted with hemophilia. It is interesting to note that hemophilia was the first disorder to be related to the X chromosome. The earliest description of its transmission by apparently normal females to affected males was made by a Philadelphia physician, Dr. Otto, in 1813. The first known bleeder in the United States, a male resident of Ipswich, Massachusetts, had about twenty hemophilic descendants over a period of 170 years (and seven generations). The other sex-linked disorders, including those listed in Table 9-1, are inherited in the same characteristic manner.

We see that when a female carrier (heterozygote) of the hemophilic gene

mutation marries a normal male, the probabilities are that the trait will be passed on to one half of the male offspring (who will be phenotypically and clinically affected) and to one half of the female offspring (who will show no clinical disease but will, like the mother, be heterozygous carriers of the trait). If the affected male with hemophilia marries a normal female, he will then transmit the abnormal gene to all of his daughters. The only X he can contribute will carry the hemophilic mutation, and since this X is contributed only to his daughters, all of his sons will be normal. The trait, then, is never transmitted directly from father to son.

Many hemophiliacs do not have distinctive family histories but are detected because of bleeding in the newborn, generally following circumcision. In these cases (roughly about 20% of the hemophiliacs born annually in the United States), a mutation probably has occurred in a maternal or paternal germ cell, resulting in either a carrier female or an affected male. (The mutation would necessarily have been in the ovum if the male was affected, but a female carrier might result from mutations in either parent's gametes.) Counseling of such families would then ordinarily involve studies of both mother *and* affected sons to determine whether the mother was a heterozygote. We will discuss the detection of carriers of the sex-linked disorders later in the chapter.

MARY LYON HYPOTHESIS

The roles of the X and Y chromosomes in sex determination and the inactivation of one of the X chromosomes in the female were discussed in the preceding chapter. In discussing the abnormalities of the sex chromosomes, we avoided one of the major problems that has intrigued geneticists. This problem may be stated as a question: "Why isn't the male seriously disadvantaged, relative to the female, in having only one 'dose' of genes located on the X chromosome while the female has a 'double dose' of the same genes?" Except for the difference in sex hormones, which is, of course, related to the male and female gonads, there is no real biochemical or physiological difference between males and females. Indeed, there is no difference between normal males and females in the level of the measurable enzymes, such as antihemophilic globulin (AHG) and glucose-6-phosphate dehydrogenase (G-6-PD), which products are, we know, related to X-linked genes. Conversely, the rarely seen female who is homozygous for one of the sex-linked disorders, such as color blindness, is not more seriously affected than the hemizygous, color blind male. The answer seems to lie in the "Lyonization" of the X chromosome: the genetic inactivation of one of the female's two X chromosomes.

Several investigators, working in different areas of genetics, supplied the evidence for the Mary Lyon hypothesis, but Dr. Lyon first derived the concept that has far-reaching significance for genetics. She noted that the female house mouse, *Mus musculus L.*, heterozygous for any one of the group of well-known X-linked coat color mutations (mottled, tortoise-shell, dappled, among others), has

Table 9-1. Sex-linked disorders

Disorder	*Etiology and clinical findings*	*Prognosis*	*The heterozygote "carrier"*
Agammaglobulinemia (Bruton's X-linked disease)	Failure of synthesis of gamma globulin; increased susceptibility to infections	Manifest in childhood; can be successfully treated with gamma globulin	Female carrier cannot be detected by present methods
Aldrich syndrome	Eczema; thrombocytopenia; dysgammaglobulinemia; susceptibility to bacterial infections	Occurs in infancy; generally, early death in affected boys	Several carriers reported to have decreased platelet levels
Anhidrotic ectodermal dysplasia	Inability to sweat (absence of sweat glands), sparsity of hair, hypoplastic nails, and absent teeth	Heat intolerance may cause death in infancy	Carriers may show malformation of teeth and mild abnormalities of teeth and breasts; "patchy" skin involvement in heterozygotes
Christmas disease (PTC deficiency)	Deficiency of PTC factor in blood; defect in coagulation mechanism	Similar to classic hemophilia, but very often "milder" in its symptomatology	Carriers may have decreased levels of PTC (factor IX)
Color blindness (red-green)	8% of males are color blind; 17% of females are heterozygous	No associated problems except at stoplights	A few females may show color vision defect, but generally not detectable
Diabetes insipidus	Failure of kidneys to respond to the pituitary antidiuretic hormone; polyuria; polydypsia	Life expectancy can be normal with adequate fluid intake; dehydration may be fatal in infancy	Carriers not detectable
Duchenne type muscular dystrophy	Progressive weakness and atrophy of skeletal muscle; "pseudohypertrophy," especially of calf muscles, is feature of this disease	Early onset with steady progression to severe muscular atrophy and disability	Some carrier females may be detected by presence of increased creatine phosphokinase levels in plasma; other carriers also may show microscopic changes in histologic sections of muscle biopsies

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency	Hemolytic anemia due to enzyme-deficient red cells; in Negroes is almost always induced by drug ingestion	Generally no difficulty except associated with drug administration; chronic anemia in variants of the disease that are found in Sephardic Jews and some Mediterranean people	Heterozygote shows mosaicism of red blood cell (G-6-PD) enzyme activity
Hydrocephalus	Sex-linked type involves stenosis of the sylvian aqueduct	Congenital hydrocephalus, of course, may have many causes and be part of such other disorders as Hurler's syndrome	Heterozygotes not affected
Ichthyosis vulgaris	Scaly and keratotic changes in skin, especially extensor surfaces of extremities	Chronic skin lesions; may progress to alligator skin condition	Heterozygotes may have dryness of skin, occasional scaling; variant of this skin disorder may appear *only* in females
Menke's syndrome	Degenerative disorder of central nervous system associated with growth retardation and peculiar stubby white hair; elevated glutamic acid in plasma	Rapidly progresses to profound mental retardation	Heterozygotes apparently not affected
Retinitis pigmentosa	Degeneration of retina with night blindness, narrowing of visual field, and optic atrophy	Frequently begins at puberty with progression toward ultimate complete blindness	Female carriers have night blindness and variable forms of the retinitis, including an intermediate form tapetal reflex
Xg^a blood group	Only X-linked blood group; 60% of males are Xg^a+	Not associated with any disease state	Thus far is only exception to Mary Lyon hypothesis; heterozygote is Xg^a+

patches of normal color and patches of the mutant color. The coat color is never completely one color or the other, and, most importantly, it is never an intermediate shade. Male mice (and mice with an XO sex chromosomal constitution) do not show this patchy distribution of hair color. Dr. Lyon hypothesized that in the somatic cells of the female mouse, one of the X chromosomes is genetically and functionally inactivated. The implications of this hypothesis now, of course, have been applied to other mammalian females, including humans.

Apparently, it is a matter of pure chance as to whether the maternal X chromosome or the paternal X chromosome is inactivated in any one cell. Further, it appears that the inactivation process occurs early in embryonic life. The evidence for this is that Barr bodies are first observable in normal females at about 12 to 16 days of fetal life. Thus, both X chromosomes and their complement of genes may normally be operative (at least for a while) in the female. The fact that both X chromosomes are functioning for at least a short time may explain the abnormalities that occur in individuals who are deficient in an X chromosome, such as in the Turner's syndrome, and in those individuals who have supernumerary X chromosomes. It seems that a double dose of the X genes is necessary for normal feminization.

The exquisite cytologic studies of Dr. Susumu Ohno demonstrated the heteropyknotic changes (the condensation and coiling up of the chromatin) in one of the X chromosomes of the female. These changes ultimately result in the formation of the Barr body, or sex chromatin mass, visible in the interphase nucleus of somatic cells. This work gave much support to the Lyon hypothesis. We discussed in Chapter 2 the relationship of the Barr body (and the late-replicating hot X chromosome visible in autoradiographic studies) to the number of X chromosomes in the sex constitution of the individual. The Lyon hypothesis most likely explains the problems of X gene dosage. The clinical implication of this hypothesis is the subject of the next section.

ALL FEMALES ARE MOSAICS

Acceptance of the concept of random and early inactivation of one of the X chromosomes in females implies that each female is a mosaic, made up of two populations of cells, each differing in sex-linked traits for which she is heterozygotic. Some cells express the activity of the paternal X chromosome, while the others express the traits of the maternal X chromosome. The human female, unlike *Mus musculus L.,* unfortunately, has no readily identifiable gene that is sex-linked. There are, however, other examinable traits that demonstrate this dimorphism of the X chromosome. The female heterozygote for G-6-PD enzyme deficiency, the Duchenne type of muscular dystrophy, hemophilia, and other disorders, now can be detected by certain laboratory procedures. A number of the sex-linked disorders are summarized in Table 9-1, but we will discuss hemophilia in a little more detail, since this disorder does typify both the hereditary aspects and the clinical importance of detection of the female heterozygote.

HEMOPHILIA

Deficiency of the antihemophilic factor (sometimes called AHF, Factor VIII, or AHG) causes the hemorrhagic disorder, hemophilia. Although hemophilia makes up about 90% of the known congenital coagulation disorders, one must be able to differentiate it from some of the other congenital clotting defects, because the hereditary patterns involved and the clinical variations are different. Some of the other congenital blood-coagulation defects are listed in Table 9-2. The number of such possible hereditary clotting deficiencies only hints at the complexities of the blood coagulation mechanisms. The hematologist, with his array of tests for these different coagulation factors, will be needed to pinpoint the missing factor so that an appropriate therapeutic regimen and the proper genetic risks can be given.

The classic type of hemophilia represents a failure in the synthesis of antihemophilic factor (AHF), a protein manufactured in the liver. This protein is so labile that it is present only in fresh (or fresh frozen) human plasma; the titer (or plasma level) of AHF rapidly decreases when unfrozen whole blood or plasma is stored. The antihemophilic factor is necessary for the clotting process that probably occurs during the stage of the conversion of prothrombin to thrombin. This process, as it relates to hemorrhagic problems, is explained in detail in several excellent texts listed at the end of the chapter. Abnormalities of this process cause a serious delay in clotting of the blood following an injury. Thus, the hemophiliac is a bleeder following almost any sort of trauma. Interestingly enough, the actual bleeding in hemophilia, as measured by capillary and platelet functions, is normal; it is the clotting time, dependent upon the complex coagulation factors, that is grossly abnormal.

The severity of the disease seems to vary from family to family. In families typifying severe hemophilia, the affected individuals have a very low titer of antihemophilic factor, or, in some cases, the factor may be absent altogether. In these individuals, spontaneous bleeding episodes are frequent. There are also families whose affected members have a mild form of the disease and in whom there may be significant titers of the AHF. An important fact for the physician to realize is that all hemophiliacs are not alike in their clinical manifestations of the disease; the prognoses, also, may vary from family to family. The hematologist's evaluation of the coagulation studies, in addition to clinical observations, may be of great benefit to a family.

Since the maternal antihemophilic factor apparently does not cross the placenta, the newborn hemophiliac is not protected as was once believed. Difficult deliveries have serious consequences for some of these children. In many other cases, circumcision is the first trauma to the hemophiliac infant, and this generally will be the first bleeding episode of his life. This episode marks the beginning of recurrent episodes of bleeding—bleding into the joints, with resulting deformities, ankyloses, and permanent crippling; bleeding into about every tissue of the body, including often-fatal intracranial hemorrhage. Again, the so-

Table 9-2. Hereditary coagulation disorders

Disorders	*Heredity*	*Incidence*	*Manifestations*	*Therapy*
Hemophilia (Factor VIII, AHF, AHG deficiency)	Sex-linked	1/10,000 males (1 in 5,000 females are carriers)	Traumatic-type hemorrhage; there is a mild form of the disease	Fresh frozen plasma; AHG concentrates
Christmas disease (Factor IX, PTC deficiency, hemophilia B)	Sex-linked	Incidence is about 20% that of hemophilia	Similar to AHG deficiency	Fresh frozen plasma
PTA deficiency (Factor XI)	Autosomal-dominant	Rare (preponderantly in Jewish patients)	Mild bleeding tendency	Only rarely requires treatment; then, plasma or blood
von Willebrand's disease ("pseudohemophilia")	Autosomal-dominant (varying degree of expression)	1/80,000	Purpuric type of bleeding; epistaxis; less severe with increasing age	Rarely requires treatment with plasma or fresh blood
Prothrombin deficiency	Autosomal-recessive	Extremely rare	Resembles mild hemophilia	Fresh frozen plasma
Proaccelerin deficiency (Factor V)		30-35 cases reported	Mucous membrane bleeding; epistaxis; associated syndactylism	Fresh frozen plasma
Proconvertin deficiency (Factor VII)		Very rare; most cases of European origin	Severe bleeding; hemarthroses	Fresh frozen plasma
Stuart-Prower (Factor X) deficiency		Very rare, limited to a few families	Varies from mild bleeding tendency to picture resembling hemophilia	Fresh frozen plasma
Afibrinogenemia, congenital		About 60 reported cases	Severe bleeding in infancy; generally milder bleeding tendency after childhood	Fibrinogen

called mild hemophiliacs may have relatively little excessive bleeding, even following trauma. Needless to say, death from exsanguination is almost unheard of in this age of modern transfusion techniques and facilities. In fact, major surgical procedures, not to mention tooth extractions and appendectomies, have become practically routine with proper preparations and precautions. Correction of the bleeding defect in hemophilia is temporarily made possible by utilizing plasma and the new concentrates and cryoprecipitates of antihemophiliac factors. Thus, the bleeding problems of classical hemophilia, as well as most of the other hereditary hemorrhagic disorders we have mentioned, can now be readily handled as far as the actual bleeding episode is concerned. The psychological problems are another matter.

Counseling considerations

As a child, the hemophiliac is constantly faced with the prospect of bleeding episodes that result in pain, disability, and frequent hospitalizations. Parents of the hemophiliac child may often react to the constant threat to a child's life by imposing strong restrictions on the activities of the child. Overprotectiveness, which may at first be related to physical dangers that will cause bleeding, can extend to all aspects of the child's management. The parent, particularly the mother, may never make any demands on the child's social development. The only prohibition, as such, is that the child cannot engage in any play, work, or self-help activities that might conceivably produce a physical hurt. Because the protective relationship is so strong and because a father is sometimes rougher in his interaction with a boy, the mother can even arrange her protective umbrella to cover only the boy and herself. The father becomes an outsider, and the family becomes divided.

Very often, as we see in families with overprotective parents, the ambivalence engendered by permissiveness and extreme restrictiveness results in rebellious behavior by the child. Among older hemophiliac children, extraordinary "acting out" behavior might even help the child to rule the family by fear. He may subject himself to physical dangers, perhaps to the point of actually hurting himself, so that the parents will accede to his wishes. One of our own patients was hospitalized twice within a few months because of hemorrhages. On the first occasion, he suffered an injury from a judo bout, and on the second occasion, he pushed his arm through a plate glass window. Because of the boy's age and the long-standing inappropriate parental management, psychiatric intervention was needed in this case.

It is thus evident that counseling directed to the parents and even to the child is an important aspect of the treatment and management of hemophilia. We feel it best to counter the psychological complications of hemophilia by encouraging the parents to set up reasonable, but safe, expectations for their child's activities. Boys can take part in many activities that are not physically harmful. The energies of boyhood have to be channeled into activities that prepare the boy to be a man;

they cannot be "used up" when the boy is always closeted in the home. Although some children may need home tutors or some other special enducational arrangements, we encourage most of our parents to keep hemophiliac children in regular schools and in a regular class. In this way boys can avoid the stigma of being considered sickly, shut-in children.

Attempts should be made to encourage the parents to provide long-range realistic opportunities for the hemophiliac child. Planning for the child's future as an adult not only promotes positive immediate actions by the family but also fosters the child's active participation in these actions. For example, because chronic bleeding may become more prevalent with the boy's increased weight, eating habits established by the child can help to keep his weight within reasonable limits. Frequent spontaneous bleeding into the joints may be partially avoided by this simple regimen. In similar fashion the hemophiliac child can develop the habit of selecting activities that, even though appropriate for a boy, are less strenuous. As an adult, he then is more likely to accept vocations and avocations that are relatively sedentary.

While we have chosen to emphasize the psychological aspects of hemophilia only, the other sex-linked disorders—such as the Duchenne type of muscular dystrophy—will demand similar concerns. Even color blindness, which is a relatively benign genetic disorder, imposes life-long limitations that should be considered by the counselor and the family. Many occupations are not suitable for color blind adults. Sometimes the "right" to drive an automobile may be curbed.

The female hemophiliac

In our discussion of the hereditary patterns of hemophilia (representing all the sex-linked disorders) we did not include the possibility of marriage between an affected male and a carrier female. In such a case, which is quite a rare occurrence, we could predict that half of the female offspring, as well as half of the male offspring, would be hemophiliacs. Undoubtedly, several of the reported hemophiliac females represent the offspring of such chance matings. The mating of an affected male with a carrier female is also responsible for the instances of color blindness, muscular dystrophy, and other X-linked disorders among females.

Hemophilia in a female also might result from her having only one X chromosome (as in Turner's or XO syndrome), or from her losing part of the X chromosome (as in an X chromosome deletion or ring formation). In these rare individuals with a nondisjunction chromosome abnormality, the X chromosome may serve as a marker indicating where the nondisjunction accident took place. Substituting another disorder, color blindness, for an example, we could speculate that in the color blind female with an XO karyotype, if the father is color blind, the father must have contributed the X with the mutant gene. Thus, the nondisjunction had to occur in the maternal gamete, the ovum. On the other hand, if the father of a child with Turner's syndrome and color blindness is normal, then he could not have contributed the X chromosome with the mutant gene for color

blindness. Since he did not contribute a Y chromosome either, the nondisjunction must have occurred in the sperm.

The next genetic mechanism we can put forth to explain the rare occurrence of a female hemophiliac, or a female with color blindness or G-6-PD deficiency and so on, is suggested by the Mary Lyon hypothesis: a female with these disorders may have mosaicism of one of the X chromosomes. Thus, we come to a discussion of the female heterozygote for X-linked traits.

The female carrier

Although female carriers are most frequently asymptomatic, bleeding tendencies—most often mild—have been recognized in hemophiliac carriers. Assays of the AHF in such heterozygotes demonstrate significant reductions in the level of the factor. We might relate the amount of AHF produced by the liver to the number of liver cells with the X chromosome carrying the mutant hemophiliac gene that is genetically inactivated (corresponding to the Barr body). If there is a relatively low level of AHF in a carrier, we could speculate that by chance most of the normal X chromosomes have been inactivated. If occasionally there is a low enough level to produce all the symptomatology of a true hemophiliac, we could again speculate that early in embryonic life most of the normal X chromosomes were inactivated. In the average carrier roughly one half of the cells would be normal and one half would have the defective X chromosome. Even in these persons there would be no evidence of a bleeding disorder, since an AHF value as low as 50% of the normal level would not lead to any obvious bleeding dyscrasia. In fact, in the vast majority of carriers, despite a decrease of AHF factor, one only occasionally finds a value as low as 50%. Indeed, many carriers have concentrations of AHF factor in the normal range.

The measurement of AHF titers in the female carrier is not altogether reliable. One of the more common problems in our clinic is that of determining whether the mother of an affected boy or the soon-to-be married sisters of the boy are carriers. Very often, low titers can be demonstrated, suggesting the carrier state; however, normal levels do not necessarily indicate that the female is *not* a carrier. Therefore, we have to use this information with great caution.

Having identified a patient as a carrier, the counselor must consider whether she should be advised not to have children—or whether, after the birth of one or more affected boys, she should be advised to stop having children. Obviously the risks are high for the offspring of the female carrier of the hemophiliac gene. One can only speculate about the number of hemophiliacs in this country today whose ancestors (similar to the case in Ipswich) promulgated this quite harmful gene. Despite our modern advances in the medical treatment of hemophilia, we still have not overcome the disabilities, the expense of frequent hospitalizations, and the emotionally crippling aspects of the disease.

As for the other genetic diseases, the consideration of risk figures will depend upon the individual family. Among Queen Victoria's offspring, it is obvious that

death through injuries had more effect on the attrition of carriers or afflicted males than did eugenic considerations. Many parents consider that the production of children, and especially boys, more than offsets the genetic risks. The counselor cannot generalize about which parents will place a heavy emphasis on risks and which parents will ignore them. His best approach is to help all parents appreciate the importance of the risk figures by understanding the seriousness of the disease. Sometimes he may be surprised to find that even those people supposedly unreceptive to genetic counseling will profit from this approach. A poor, uneducated mother herself suggested to us that she have a tubal ligation after we apprised her of the consequences of hemophilia for her two daughters and her hemophilic son. We supported the idea, but even without our encouragement, she was firmly convinced that this was the right step.

The variability of expression of certain sex-linked disorders in the female carrier (as a consequence of the random inactivation of one of her X chromosomes) may help the genetic counselor in several other fairly common problems. In fact, Ernest Beutler's study of the carriers of G-6-PD deficiency, performed almost at the same time as Dr. Lyon's observations in mice were published, supplied the first clinical proof of mosaicism in human females. Beutler demonstrated that the heterozygous female had two populations of red blood cells, one consisting of cells with normal enzyme activity and the other of cells with absent or markedly decreased G-6-PD activity. These heterozygous females, then, had an intermediate level of G-6-PD enzyme activity, frequently in the range of 50% of the norm—sufficient to prevent the symptomatology of the disease. This level is rarely demonstrable by the use of laboratory procedures, however. This indicates not only that it is necessary to study the red cell enzyme activity of the child admitted to the emergency room with mothball poisoning that results in induced hemolytic anemia, but also that one should examine the red blood cells of the child's mother and of the child's siblings.

The G-6-PD deficient individual is extraordinarily susceptible to such ordinarily relatively harmless drugs as primaquine, acetanilid, and the sulfonamides. Recognition of this hereditary disease should enable the physician to advise the family to avoid using drugs that might induce the clinical illness. The importance of such advice cannot be overemphasized, since the rate of G-6-PD deficiency in American Negroes is about 10%, and there is a "non-Negro" type with high rates among subpopulations in the Mediterranean area and among Sephardic Jews.

Several of the other X-linked disorders, for which there have been successes in demonstrating double populations of cells in the female heterozygote, are briefly summarized in Table 9-1. These include the Duchenne type of muscular dystrophy, which is characterized by a progressive atrophy of muscle. This disease is often preceded by an enlargement of some muscles (primarily calf muscles)—pseudohypertrophy actually representing replacement of muscle mass by fat and swollen muscle fibers. The disease develops in boys in the first few years of life,

progresses to complete invalidism and, frequently, to respiratory death because of weakness of the diaphragm and intercostal muscles. During the early stages of the disease—the time of muscle atrophy and breakdown—high levels of creatine kinase are found in the serum. These high levels result from having been lost from the damaged muscle cells.

Although carriers only very rarely show clinical muscle weakness, many do show an elevation of the serum kinase levels. On muscle biopsy, some even show the early changes of the dystrophy: a vacuolization of the muscle fibers. Thus, the carrier of the X-linked muscular dystrophy may be identified, just as in hemophilia. Again, however, there is no consistency in these findings, and many carriers may have completely normal creatine kinase levels and normal muscle tissue. It is obvious, though, that the poor prognosis of the sex-linked variety of muscular dystrophy makes it mandatory that the physician diagnose the disease correctly by differentiating it from the other variants of muscular dystrophy, many of which have different prognoses and different hereditary patterns. The other forms of muscular dystrophy may be autosomal-recessive or autosomal-dominant in nature.

In the table listing some of the X-linked disorders, we included other diseases for which the heterozygote may be detected, and for which one can see the effect of X chromosome mosaicism in females.

X-LINKED DOMINANT DISEASES

It should be mentioned that several X-linked diseases, including the hypophosphatemic type of vitamin D–resistant rickets, appear to have dominant hereditary patterns. In other words, the heterozygous female is clinically affected; and when she marries a normal male, we can predict that half of the children of both sexes will be affected. If, contrariwise, the affected male mates with a normal female, the sons will necessarily be unaffected, while all the daughters will have the disease.

HAIRY EARS AND THE Y CHROMOSOME

We have discussed the detection of the heterozygote in the X-linked disorders, such as hemophilia and muscular dystrophy. Heterozygosity in most cases is difficult or sometimes impossible to demonstrate. Y-linked hereditary factors, however, should be very obvious phenotypically. The pedigree reflects the obvious heredity of Y-linked diseases by the fact that only sons have been affected, and no daughters have been affected or found to be carriers of the trait. Except for the males of an eighteenth century circus family, the Lamberts, who exhibited themselves as "porcupine men," and some family groups in India and Israel with hairy pinnae (ear rims), there has been no linkage of any traits with the Y chromosome. Indeed, the Lamberts seemed to have invented affected males for their pedigree, so that the hairy ears gene seems to be about the only factor, other than testicular development, present on the Y chromosome. We refer the reader

to the article by Sarkar and associates for a photograph of hairy ears, ranging from single hairs to massive tufts.

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Chapter 10

Twins, heredity, and blood groups

Throughout history the birth of twins has been greeted with special signs of social concern. In some historical periods the birth of twins has been interpreted as a sign of divine displeasure; in others periods, a divine blessing. Even in recent times, twins are not viewed by all peoples with the same general approval that we show in the United States. Some primitive tribes with limited food supplies kill one of the twins. Other tribes, aware of the complications to the mother who gives birth to twins, view twins as a hazardous curse to their mothers and undesirable as future marriage partners.

Perhaps, in the United States, we accord twinning a special social approval because of the relative infrequency of the event. This approval certainly seems forthcoming for other degrees of multiple births. The birth of triplets, which occurs about once in 8,000 to 10,000 births, is newsworthy at least at a local level. The birth of quadruplets, said to occur about once in 300,000 to 600,000 births, may make national headlines; and the birth of quintuplets, occurring once in more than 25,000,000 births, establishes the family as international celebrities. Multiple births of six children or more are extremely rare, and few verifiable cases are on record. One fairly well-documented case, in which thirteen children were born at one time, concerns the noble family Trazegines of France. One of the thirteen children, all of whom lived, accompanied Saint Louis on a crusade to Palestine in the thirteenth century and later became Constable of France.

The interest that the medical geneticist has in twins or other forms of multiple births comes from two sources. He is interested in whether the presence of multiple births is a phenomenon resulting from hereditary influences—i.e., he wants to know if the production of twins seems to run in families. The medical geneticist's second interest in twins is that they provide an experiment in nature by which he can determine how much weight or influence heredity or environment exerts on a number of subtle human attributes. Since there is an irrevocable interaction of genetic and environmental factors for all people in all situations, we can explore one factor or the other by selectively suppressing the influence of one

factor or the other. The interaction of these factors was touched upon in Chapter 4 under the topic of multifactorial or polygenic factors of heredity.

TYPES OF TWINS

The biologic situations that could result in twins are commonly those in which either two ova have been fertilized by spermatozoa or a single ovum, fertilized by a single sperm, has divided at some early developmental stage. The binovular twins, those coming from the two fertilized eggs, may be alike or unalike in sex (since the two sperm may contribute the same or different sex chromosomes). These twins are called *dizygous* or fraternal twins. The second type of twins, the *monozygous* or identical twins, results from the single fertilized ovum. These twins are always alike in sex because the single sperm has contributed but a single sex chromosome. The important distinction between these two types of twins is that the monozygotic twins have identical genotypes, whereas dizygotic twins have genotypes no more similar than siblings born at different times. In other words, the monozygotic twins should be exactly alike in their genetic material, but the dizygotic twins should be no more alike than, say, one child and his younger brother or sister. This distinction is an important one, as we will see when we discuss the influence of heredity and environment.

Generally, the monozygotic and dizygotic twins differ in two other respects: in their placentation and in their membranous structures (fetal membranes). Placentation—or the manner in which the placenta is attached to the uterus—and the structure of the inner and outer membranes (amnion and chorion) making up the placenta are partial guides for determining zygosity. Dizygotic twinning usually results in two placentas, each of which has its own amnion and chorion. Even when the two placentas are completely fused, so that it appears that there is but one placenta, there will be two amnions and two chorions. The two chorions may be so fused, however, that they can be distinguished only by histologic examination of the placenta, which would not ordinarily be performed. These structural differences are shown in Fig. 10-1.

For monozygotic twins the picture is complicated by the time at which the division of the single fertilized ovum occurs. If the division occurs before the pretwin embryo is implanted on the uterus lining, then, when implantation occurs, there will be two placentas with two amnions and two chorions. If the division occurs during or after the pretwin embryo is implanted, varying degrees of placental fusion will result. The usual consequence is that each twin has a separate amnion within a single outer chorion. Thus monozygotic twins may have one or two chorions. The presence of one chorion is generally accepted as evidence for monozygosity, primarily because there has never been a report of unlike-sexed twins who had a monochorionic placenta. The presence of two chorions makes it likely that the twins are dizygotic, but not assuredly so. The present evidence is that about 15% to 26% of monozygotic twins have two chorions.

Without considering other factors, the determination of zygosity by examining

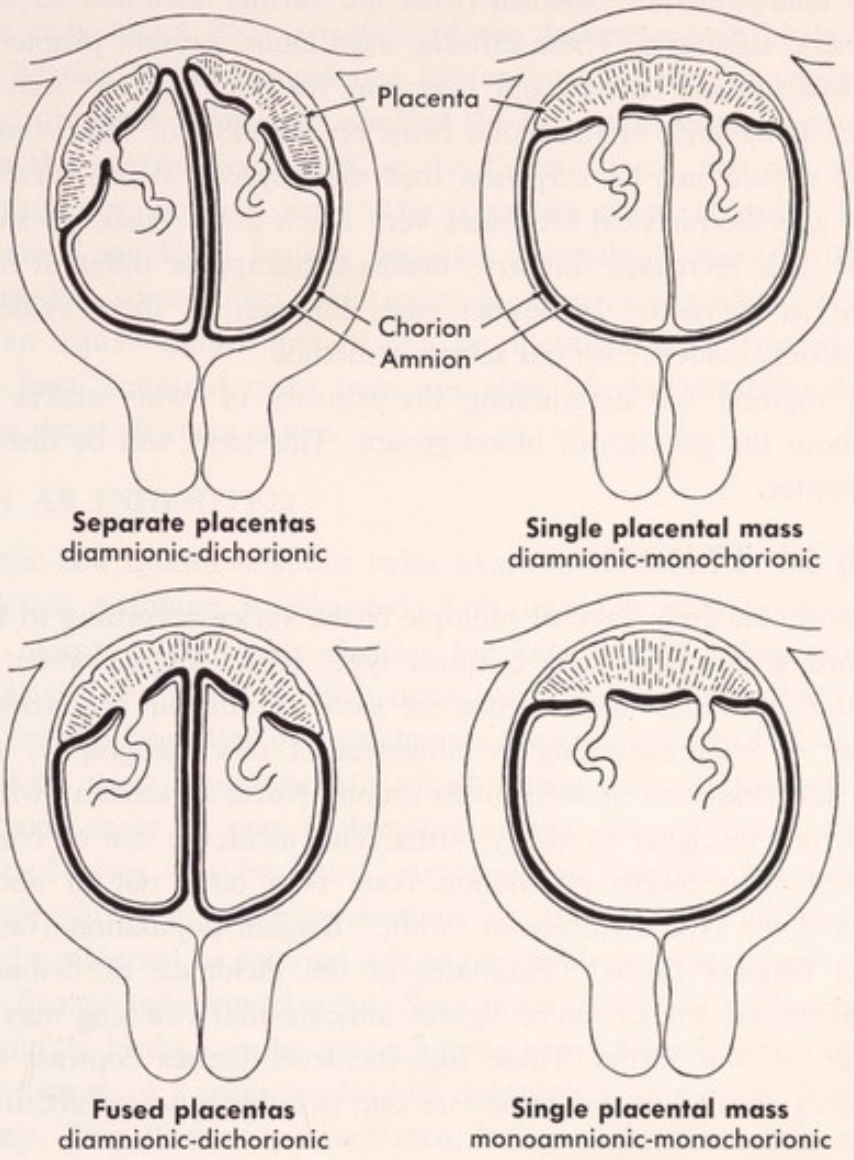

Fig. 10-1. Determination of the zygosity of twins by examination of the fetal membranes. (Courtesy Dr. F. Falkner, Louisville, Ky.)

the placenta and the fetal membranes is generally unreliable. Moreover, in many cases we do not have even this information available, since many physicians delivering twins make no note of these considerations. Other factors related to the zygosity of twins must be considered.

The most obvious and easiest determination of dizygotic twins can be made when the twins are sexually different; they cannot be monozygotic or identical twins by definition. Some other criteria for the identity of monozygotic twins include remarkable similarities in hair color and texture, pigmentation of the eye (although distribution of nevi may differ), skin complexion, amount and distribution of body hair, dental development, proportions of limbs, facial features, and general appearance. Finger and palm prints may be very helpful. Since it is assumed that many genetic factors determine these characteristics, striking similari-

ties of these characteristics between twins are further assumed to be indicative of a high genetic similarity. These criteria, used alone, present problems for those performing twin studies, because our reasoning for monozygosity may tend to become circular. If we pick monozygotic twins on the basis of their similar physical attributes, we should not be surprised that monozygotic twins, identified in this fashion, have specific physical attributes very much alike. Also, we should not be surprised that their increased similarity makes them appear different from another group labeled as dizygotic. In neither case, however, is there evidence for zygosity; there is only evidence for our selection method.

A useful method for determining the zygosity of twins makes use of our knowledge about the genetics of blood groups. This topic will be discussed at the end of this chapter.

INCIDENCE OF TWINNING

As we know, the frequency of multiple births varies according to the numbers of infants born. Twins, the most frequent type, occur roughly about once in 86 births—yet this incidence figure is not the same throughout the world. The incidence appears to vary according to influences of race, geography, and climate; for example, the incidence of twin births among North American "white" populations is about one in eighty to ninety births. This incidence can be compared with the North American Negro population (one twin birth out of about seventy-one births) and the North European "white" Belgian population (one twin birth out of about fifty-six births). Estimates of the incidence of twinning in some African countries are higher; some figures indicate that twinning may occur once in every three to four births. These high-incidence figures contrast sharply with incidence figures applied to the Japanese: one twin birth out of about 140 to 150 births.

It should be noted that all of these incidence figures are applicable only at birth. Multiple birth constitutes a hazard to life, and early death is commoner among twins than among singletons. The hazards presented to twins are those related to a presumed interference of one fetus with another, malpresentation during delivery, and the effects of low birth weight. If we concern ourself with the incidence of living twins, the appropriate figure is more like one out of approximately one hundred instead of one out of eighty-six.

Incidence figures may also vary due to the effect of maternal age. The frequency of the birth of twins to women past the age of 20 increases sharply with increasing maternal age. Then the frequency drops off again after reaching a maximum when women are between the ages of 35 and 39. This effect has been noted for both "whites" and Negroes in the United States.

The incidence of twin type is known to vary also. Among the "white" population in the United States, fraternal twins make up about 66% of all twin births. The percentage of fraternal twins among the Negro population is estimated to be about 71%—yet in Japan, where the incidence of twinning is quite low, it is

estimated that most of the twins are identical twins. Fraternal twins are estimated to constitute only about 25% to 40% of the Japanese twin births.

The application of these incidence figures in counseling is generally straightforward. The pregnant woman apprised of the fact that she may have a twin birth can be given the general figure that, in the United States, one out of about three twin births produces identical twins. The counselor must recognize, however, that these are general incidence figures, because, interestingly enough, the age of the mother again has some effect. For example, a woman under 20 years of age has about an equal chance for having an identical or a fraternal twin. The tendency to have fraternal twins increases after 20, but starts to decrease after the woman is about 40 years of age.

TWINNING AS INHERITED

One of the few questions about twins likely to be asked of the genetic counselor is whether twinning is inherited. This question may take two forms: a couple may inquire about their chances for having twins when some ancestors or relatives have been noted to have twins; or a couple having had one or more sets of twins may be interested in their chances for a recurrence of twins.

The reasons these questions are asked spring from commonplace observations that twins seem to run in families or that among many siblings, more than one set of twins may be found. Among some families, we may notice that twinning occurs in every other generation; in other families, twins found in the offspring of the maternal or paternal side of the family may be regarded as "certain" evidence for further twinning to occur. Such observations, as well as those pertaining to all multiple births, can be found among many historical accounts. Aristotle reported the history of a woman who had quintuplets four times. Pliny reported a similar history. Two Russian peasant men, living in the nineteenth century, have been noted to have had families with a preponderance of multiple births. One peasant, who was presented to the Czarina of Russia, had had four sets of quadruplets, eight sets of triplets, and nine sets of twins by two wives! The other peasant, also twice married, had sired eighty-seven children consisting of at least twenty-four sets of twins, seven sets of triplets, and four sets of quadruplets. The more commonplace observations of several sets of twins in the family pedigree are so numerous that it is difficult to refute the obvious; twinning must be genetically determined.

The pedigree data on twin births, however, do not indicate that the inheritance of twinning is an unqualified fact. Statistical analyses of these data show some tendency for certain families to show clusters of twin births. Also, there is a tendency for some mothers who have had twins to show a higher frequency of twin births among their other children. But the interesting aspect of these data is that the tendency to have twins in the family line and the tendency to have twins repeated within a family are related to the presence of fraternal twins only. Mothers of identical twins appear to show no more tendency to have another set of twins

than other women in the general population. Also, identical twinning has little or no tendency to reappear in family pedigrees. Mothers of fraternal twins, however, have two to three times as much chance for having another twin birth as women in the general population. Furthermore, pedigrees with fraternal twins have a pronounced tendency to have fraternal twins reoccur. Relatives of fraternal twins also show these same tendencies.

The genetic counselor should be able to use these figures quite easily. Couples with pedigrees showing instances of fraternal twin births have a better chance of producing twins than the chance of once in eighty to ninety births found in the general population. Also, the couple who have already had a fraternal twin birth have, as we have indicated, a higher chance for another twin birth than is found in the general population.

TWINS AS AN EXPERIMENT

Human geneticists have long since given up the idea that poor protoplasm, passed from one generation to the next, accounts for most of man's medical and social ills. It is no longer considered reasonable to assume that all ignorance, poverty, disease, and crime result from bad genetic material alone. The appeal of the simple Mendelian rules of inheritance for explaining human failures (and successes) remains, but we now know that much more subtle aspects of heredity have to be explored. The new look at heredity also has prompted closer attention to environmental agents that, alone or in combination with genetic factors, produce variations in humans.

The controversy that once raged about the relative influence of heredity and environment, nature versus nurture, has taken many twists over the years. In its simpler form, the debate has produced strong arguments for heredity and equally strong arguments for environment. Today, the controversy is certainly far from being over, but it seems to have shifted from argument to evidence, part of which comes from twin studies.

Twins, because of their genetic identities, have provided human genetics with a type of natural experiment. The logic of the experiment is relatively simple. Identical twins have identical genotypes. To the extent that human characteristics are genetically determined, identical twins should most share these characteristics—i.e., identical twins should show a high degree of *concordance*. Fraternal twins, on the other hand, although born at the same time, are no more genetically alike than siblings. Therefore, they should share genetically determined characteristics no more than siblings. Fraternal twins, then, should show more *discordance* on genetically determined characteristics than identical twins. If one assumes that the effects of environment would be the same for identical or fraternal twins reared together, then any differences found between characteristics of identical and fraternal twins should be genetic in origin. This study method obviously must assure that the fraternal twins are sexually alike, because environmental influences are different for males and females. Another approach is to study identical twins who

have been separated and raised in dissimilar environments. Intrapair differences found in these identical twins should be environmental in origin. Whatever similarities are found should be due to genetic factors. One may be reminded that a novel, *The Corsican Brothers,* by Alexandre Dumas is based on differences and uncanny similarities found in identical twins reared apart.

In the following sections, we will give some of the highlights of information about heredity available from twin studies and correlative studies of relatives. These highlights will pertain more to behavioral anomalies than to physical anomalies, since the latter will be discussed more fully in their appropriate chapters. In both cases, our use of twin data is not intended to be exhaustive. We have chosen to avoid discussing many of the relationships found between genotype commonality and such things as handedness, motor abilities, physiological, sensory, and perceptual variables. These relationships are important to genetics, but, as a rule, they are not very important to genetic counseling. In addition, some of the data presented suffers from being based on a small number of studies employing a small number of twins. Even with these limitations, the data are more than suggestive. In any event, the curious reader can turn to the suggested readings for scientific material in depth.

Intelligence

The extent to which the environment or heredity determines one's intelligence has been an important scientific and social concern for years. The "moderates" take the point of view that nature and nurture collaborate to produce the intellectual endowment that one has. This position, although timid, is appealing for social reasons alone. Unfortunately, this position has tended to obscure the remarkable consistency of data accumulated from twin studies over the years. These data would indicate that intellectual potential is certainly related to genotypic differences. This relationship can be shown by correlations between genotypic similarity and similarity on mental test performance.

In a large random-mating population, unrelated persons should have genetic correlations approaching zero. These persons should also show zero correlations on intelligence measures. Studies on large populations usually present this expected relationship. At the other extreme, identical twins should show 100% correlations if intelligence were completely determined by heredity. Observed correlations for identical twins reared together have ranged from about a 70% to 90% commonality. Identical twins reared apart show lesser relationships: the range is from about 60% to 85%. Thus, one can conclude from both of these sets of findings that genotypic similarity greatly contributes to intellectual similarity. Environment plays a lesser, but still contributory, role. By virtue of the fact that relatives will share genetic similarities to a lesser degree than identical twins, correlations greater than zero but less than unity would be expected. These relationships have been found to be consistent with trends expected from a polygenetic hypothesis.

Interestingly enough, differences in the intelligence of identical twins can be

related in small part to the birth weight of the twins. The heavier of the twin pair can be expected, on the average, to have a slight, but significant, intellectual advantage over his lighter companion. This relationship has not been found for fraternal twins. Although the nature of these differences is not fully known, it is suspected that the intrauterine environment of the twins is the determining factor.

Mental disorders

Temperament and personality have been thought throughout recorded history to be related to one's genetic heritage. Families have been noted to have a predisposition for melancholia, capriciousness, introversion, and a host of other behavioral attributes. Even today, one hears that an offspring has acquired, among other things, moodiness, stubbornness, or a violent temper from a parent or relative.

Behavioral traits have likewise been linked to other physical characteristics. Tall, thin people are said to be oriented to intellectual pursuits. They tend to be more aloof, moody, or introverted. Fat people, on the other hand, are said to be outgoing, jovial, and oriented to all the hedonistic pursuits of a Falstaff.

The commonplace observations that physical and behavioral commonalities exist and might be related to genotypic commonality now appear to have some validity. The evidence supporting these beliefs is most clearly presented in studies of such mental disorders as schizophrenia and manic-depressive psychosis.

Schizophrenia occurs in every segment of the population and will afflict at least 1.5 million of the people living in the United States today. The general expectancy rate of schizophrenia, the most common of the psychoses, is conservatively calculated to be between about 0.7% and 1.0% of the population.

The high incidence of schizophrenia has made it difficult to ascertain obvious genetic causes—yet the expression of schizophrenia in families with a schizophrenic patient indicates that the rate of incidence is higher in the kinship and varies according to the extent to which genes are in common. For example, in families having schizophrenic members, full siblings of those members have a schizophrenia rate of about 12% to 14% as compared to half-siblings, who have a rate of about 7%. Fraternal twins who, as we indicated earlier, are like full siblings in their genetic commonality, have a rate of about 15%. The highest rate, as one would expect from a genetic hypothesis, would be found for identical twins. Such is the case: identical twins have a schizophrenia rate of 86%. This rate, which is about six times the rate found for fraternal twins, is approximated in every instance, whether the twins were reared together or apart. The high concordance of schizophrenia for genetically identical persons is certainly strong evidence for a genetic influence.

This same influence is likely to be manifested in the physical characteristics or "body type" of schizophrenics because the incidence is found to be higher for the constitutionally thinner or more angular person. Whether this is evidence for an

underlying biochemical factor that is associated with physical characteristics and with schizophrenia is not clear. Also, it is not clear whether the genetic abnormality expresses itself as an incomplete dominant or recessive trait. It is clear that the empiric risk figures alone would indicate that the closer one's genetic relationship to a schizophrenic, the more likely it is that one can also have the disorder.

The literature on manic-depressive psychosis has made use of the same methods employed for studying schizophrenia. Manic-depressive or cyclic psychosis is found in about 0.4% of the general population. This psychosis has been related to such physical disorders as obesity, gout, diabetes, and cardiovascular disorders. It has also been related, with even more striking clarity than schizophrenia, to genotypic commonality. The morbidity rate is about 96% for identical twins and 26% for fraternal twins. These rates, as well as the corresponding family-risk figures, are all higher than the morbidity rates found for schizophrenia. For example, full siblings have a manic-depressive rate of about 23% as compared with the schizophrenia rate of about 12% to 14% for full siblings. Studies of cultural isolates who have high rates of consanguinity support these data in that some such isolates also show remarkably high rates of manic-depressive psychosis. Finally, studies of the offspring of manic-depressive patients would indicate that the morbidity rate is about 15%, which is almost forty times higher than the rate in the general population.

The evidence that heredity has a greater influence on manic-depressive psychosis than on schizophrenia has been attributed to a dominant gene with incomplete penetrance. This gene is thought to express itself by affecting normal metabolic stability. This would explain the disease's relation to the physical or constitutional factors.

Genetic factors that contribute to psychoneuroses have been studied less extensively than those related to the psychoses. The results from studies are still qualified by the poverty of findings, but the twin studies available indicate that heredity has a slight influence on psychoneuroses. Neurosis, as defined as a condition of social maladjustment, has a morbidity rate of about 69% for identical twins as compared to about 31% for fraternal twins. Unfortunately, these data cannot be interpreted meaningfully because the incidence of psychoneuroses in the population is poorly realized. The incidence figures available are too dependent on the cultural-social definition of these disorders. The general incidence of psychoneuroses, therefore, varies from study to study. This variability tends to obscure both genetic and nongenetic factors. The safest interpretation of the studies to date is that one should not accept or reject genetic and nongenetic explanations.

Convulsive disorders

Convulsive disorders or convulsive seizures of all types and severity are quite common. There is an incidence of about one person in 200 to 350 being affected. Such disorders, known under the names of epilepsy, convulsions, and, more colloquially, "fits" and "spells," evoke grave concern because of their relation to

serious central nervous system disorders. Also, even in modern times, social pressure and social stigma are attached to these disorders. Prohibitions concerning marriage, employment, and the operation of machinery are quite common. For this reason alone, today, as in previous times, convulsive disorders tend to be hush-hush conditions.

A genetic explanation of convulsive disorders has been entertained for the types that are called *idiopathic, constitutional,* or *cryptogenic.* These types are defined by an absence of a precipitating factor, such as an acquired disease or illness. The disorders that have a precipitating factor are usually not ascribed to genetic influence even though the precipitating factor itself may be linked to heredity. One such example would be the convulsive disorders found among children with phenylketonuria (PKU). We might say, then, that genetic hypotheses have been entertained for those convulsive disorders that can be explained in no other way.

Some studies have pointed out that specific electrical abnormalities are more likely to occur in the electroencephalograms of parents and siblings of children with cerebral dysrhythmias. Studies of identical twins indicate that their electroencephalographic tracings are similar whether or not abnormalities are present.

If clinical epilepsy is manifested in one member of identical twin sets, the other twin is affected in about 70% of the cases. Among fraternal twins the rate is only about 3%. These rates were determined by all cases of twins with convulsive disorders. When only the idiopathic type cases were considered, the morbidity rate for identical twins increased to about 86%. Full siblings demonstrate a rate of about 4%, which is comparable to the fraternal twin rate.

Other studies of families in which the parents or the children were epileptic indicate that there are familial tendencies for epilepsy. As compared with control parents and children, an epileptic parent or an epileptic child has a significantly higher likelihood for having an epileptic kinship. These empiric risk data would suggest that if a child in a family has a convulsive disorder, each subsequent child has from about an 8% to 13% chance for being similarly affected. Also, those families in which one of the parents has epilepsy have from about a 3% to 5% chance for each offspring to be epileptic. Both of these sets of chances are noted to change with the type and severity of the convulsive disorders found. Usually the genetic risk is attached to the more severe forms of convulsive disorders that occur earlier in life and are concomitant with mental retardation. For example, convulsive disorders noted in patients past the age of 30 are not likely to be associated with increased risks for their offspring.

COUNSELING CONSIDERATIONS

We have already entertained some of the questions that some people will surely raise about twinning. The chances for having twins and the chances for having a particular type of twins are not as firmly established as some of our odds cited for

dominant and recessive disorders—yet, they are useful odds and should be given to interested parents.

The questions that might be asked by parents about the influences of heredity upon intelligence and mental disorders are often avoided by parents. Perhaps this is just as well in many cases, because the answers we have are often complex and not easily interpretable from a genetic point of view. Also, as we have indicated, some of our answers must be qualified because of the paucity of valid or generally accepted findings. The family physician can take one word of caution from these findings, however. He can be alert to the possibility that when one member of a kinship exhibits an anomaly, other kinship members may present similar characteristics. The possibility of such shared characteristics is as great or as small as the degree of the genotypic relation. The counselor's alertness should be commensurate with the degree of relationship. For example, the detection of behavioral anomalies in one identical twin should make the physician extremely alert to the possibility that the other twin has or will have a similar anomaly. He should not share his dire speculations with the parents, but he should pursue a vigilant course to verify or invalidate his concerns. Similar approaches can be taken when the physician is aware that adopted children have come from parents who have been mentally retarded, psychotic, or subject to convulsive disorders. This should not be interpreted as an alarmist position, only as a cautionary one. As we have shown, even identical twins are not always going to share the disease entities discussed. That they can be shared should prevent the physician from taking a relaxed point of view that lightning cannot strike twice.

GENETICS AND BLOOD GROUPS

The expression "blood relatives" can be traced to the idea, once very popular, that heredity was determined by a mixture of the parents' blood (or the germinal fluids). Genetic determination of hereditary traits is now very clear, but certainly blood group factors (and, as we will mention later on, these now include serum protein groups and white blood cell antigens) have become very important in clinical medicine as genetic markers. The value of new techniques in serology and blood grouping lies in the fact that the blood type of an individual can now be his most precisely characterized hereditary trait; and, unlike attributes such as eye and hair color or skin complexion, the blood type will remain unchanged from the moment of birth throughout adult life. It is evident that blood groups are remarkably consistent and unaffected by environmental agents. In addition, the patterns of hereditary transmission of the blood group factors have been worked out, and in most cases they consistently follow the Mendelian principles. The constitution of the heterozygote is readily differentiated from that of the homozygote in most individuals.

We intend to use this opportunity to discuss the use of the blood groups, not only in twin zygosity studies but also in relation to some other problems in clinical practice: questions of paternity, racial differences, Rh incompatibility and blood

transfusion reactions, increased susceptibility to certain diseases, and, of increasing interest, transplantation of organs.

Blood groups

The ABO blood grouping separates human beings into four groups, by the presence or absence of these blood factors (Table 10-1)—but now there are a full dozen or so other genetically determined blood group systems, and over forty separate blood factors, some of which are listed in Table 10-2. A combination of the groups and systems presents the possibilities of millions of serologically recognizable genotypes. We know that at each of these blood group loci on the chromosome, there may be numerous allelic genes that can be detected by a battery of antisera (e.g., anti-A, anti-M, anti-Ks^a, anti-Rh). These antisera are antibodies specific for the particular blood factor.

The year that Gregor Mendel's laws of heredity were rediscovered was the same year that Landsteiner first demonstrated the individuality of the human blood groups. In 1900 he postulated that there is one of two antigens, A and B, on the red blood cells. Individuals have antibody in their serum that agglutinates B red cells (anti-B); B individuals have antibody to A (anti-A); O individuals have both antibodies. Of course, now we also know that AB individuals have no antibodies in their serum. It is clear why we speak of group AB individuals as being universal recipients, since they can be given blood transfusions from any of the ABO blood types. On the other hand, O blood donors are in great demand as universal donors. Although the O blood group originally represented the absence of any blood antigen at all, there is speculation that an O gene does exist that is recessive to A and B.

With the exception of one of the Rh blood group factors, the different blood antigens in all the blood group systems are *codominant,* which means that both alleles are always expressed and can be demonstrated with the proper techniques. The genotypes AO or BO cannot be distinguished from AA or BB respectively, however, and are recognized as A or B. Table 10-1 summarizes these observations and gives the incidence of the ABO groups in the United States.

Obviously, the consistency and remarkable serologic and immunologic characterization of the blood group factors makes them excellent markers for

Table 10-1. Incidence of ABO blood groups

Blood group phenotype	*Blood group genotype*	*Antibodies in serum*	*Incidence in United States (%)*	
			White	*Negro*
O	OO	Anti-A, anti-B	45	48
A	AA/AO	Anti-B	41	27
B	BB/BO	Anti-A	10	21
AB	AB		4	4

Table 10-2. Known blood group systems in man

System	*List of some of the antigens (alleles)*	*Comments*
ABO	A, B (O)	80% of individuals secrete ABH substance in saliva; antigens also found in plants, etc.
MNSs	M, N, S, s	Little clinical importance, except for identification
P	P_1, P_2	Useful in identification
Rh	C, c, D, E, e	Isoimmunization of mother—Rh hemolytic disease
Lutheran	Lu^a, Lu^b	First example of linkage (secretor) in man
Kell	K, k, J_s^a, J_s^b	J_s^a found only rarely in Caucasians
Lewis	Le^a, Le^b	Lewis antigens are primarily found in saliva and serum, and are absorbed onto red cells
Duffy	Fy^a, Fy^b	Fy (a-b-) phenotype rare in Caucasians
Kidd	Jk^a, Jk^b	Useful in identification
Diego	Di^a	Specific marker for individuals of Mongoloid origin
I	I, i	Not useful, since antigenicity varies with age
Auberger	Au^a	Only described since 1961
Xg	Xg^a	Only X-linked blood group

determination of twin zygosity. Ultimately it is most important in deciding whether twins are dizygotic or monozygotic for us to demonstrate any possible genetic variation. Examination of the blood group factors—generally involving the ABO, Rh, MNSs, Kell, Lewis, and Duffy groups and utilizing about fifteen to twenty individual blood group factors—will give a great percentage of correct decisions. Now, of course, we also can include the typing of such serum proteins as transferins and haptoglobins in this blood grouping. Complete serology and blood group examinations are available at many commercial laboratories in addition to the numerous university blood bank centers. A difference in any one of the blood group systems would ordinarily be enough evidence for classifying a set of twins as dizygotic rather than monozygotic.

We have seen one twin set who demonstrate the need for looking at as many traits as possible. Fig. 10-2 illustrates a 2-month-old set of twins, one obviously showing the characteristics of Down's syndrome (he had the classical trisomy 21 karyotype) and his sister showing no physical or cytogenetic abnormalities. Despite the sex and the chromosomal differences—they were thus clearly dizygotic—the blood group factors, including the Xg blood group, were identical, as shown in Table 10-3. It is obvious that by chance alone such factors may show no differ-

Table 10-3. Blood group studies in dizygotic Down's syndrome—normal twin set and*

	Grp.	*M*	*N*	*S*	*s*	*D*	*C*	*E*	*c*	*e*	*K*	*k*	*Le*^{a}
Father	0	−	+	−	+	+	+	+	+	+	−	+	−
Mother	0	+	+	+	+	+	+	+	+	+	−	+	−
Jerry	0	+	+	+	+	+	+	+	+	+	−	+	+
Terry	0	+	+	+	+	+	+	+	+	+	−	+	+

*Courtesy Drs. F. Falkner, L. Reisman, and R. Howard, Louisville, Ky.

Fig. 10-2. Male infant on the right has Down's syndrome. His twin sister has a normal cytogenetic constitution. The blood types on both children are concordant for twenty-six factors, however. (Courtesy Drs. F. Falkner, L. Reisman, and R. Howard, Louisville, Ky.)

ences in dizygotic twins, who might not be as phenotypically different as the example we have used. Such twins might be erroneously classified as monozygotic. On the other hand, mutations and chromosomal aberrations may occur in one or both siblings of a monozygotic twin set and cause obvious differences in phenotype. There are reports of monozygote XO and XY twins, mosaic trisomy 21 and normal twins, and the like. These events, however, are rare, so that blood grouping is generally a fairly conclusive method in zygosity determination.

Paternity problems

Medicolegal problems are a fascinating aspect of blood grouping. Since there is usually no doubt about identifying the mother, the problem generally is one of identifying the father. Proving paternity with certainty, like proving monozygosity, is not possible, but paternity can be disproved by finding incongruities in the blood

parents*

Fy^a	Jk^a	Mt^a	Lu^a	Lu^b	Vw	Do^a	Co^a	Gy^a	Vel	Yt^a	Xg^a	Fy^b	Jk^a
+	+	−	−	+	−	−	+	+	+	+	−	+	+
−	+	−	−	+	−	+	+	+	+	+	+	+	−
−	+	−	−	+	−	−	+	+	+	+	+	+	+
−	+	−	−	+	−	−	+	+	+	+	+	+	+

group factors. The presumptive father will be exonerated if he *and* the mother do not have a blood group factor that the child does have, or if the child does not have, for example, a red blood cell antigen that the presumed father must have transmitted. Thus, if the presumed father is AB and the mother is O, the baby cannot be type O too. Among some American Indian tribes (described by Dr. Wiener, who has contributed so much to the entire field of blood grouping and serology), in which *all* the members have type O blood, typing, of course, would not be too helpful for the accused individuals. The chances of the accused man depend, sometimes, on the ethnic distribution of blood groups. Generally, however, with the utilization of the ABO, MNS, and Rh systems, Wiener estimates that one can exonerate about one half of the men wrongly accused of paternity. Use of more blood groupings makes the chances somewhat better. One may hope—on behalf of the other half of the group, who are not excluded because of mere coincidence—that techniques in blood grouping continue to improve even more.

Racial differences in blood grouping

Blood grouping may, of course, be helpful in the rare case of a hospital nursery mixup, and we have been asked occasionally by a state adoption agency to help determine the race of a young infant to be placed for adoption. There is no real degree of accuracy in such an effort, but certain blood types may be associated with certain racial groups. For example, although the Rh factor is present in 85% of Caucasians and there is a slightly higher incidence in Negroes, it is present in just about 100% of Oriental peoples. As shown in Table 10-2, the Diego blood group factor (D_i^a) is apparently present only in Mongolians. (Interestingly enough, it is absent in the Eskimo, who presumably springs from pure Mongolian stock.) The J_k^a factor (Kell system), cDe genotype, and the FyFy genotype (Fy[a-b-] phenotype) are much more common in American Negroes than in Caucasians. The latter genotype is present in over 40% of Negroes, but very rare—about 1/1,000—in Caucasians; these findings may be helpful in solving some adoption problems.

Isoimmunization

Only the anti-A and anti-B serum antibodies occur spontaneously, possibly because of the ubiquitous nature of A and B substances mentioned previously. The

other antibodies are found only after *isoimmunization* or sensitization of the individual with incompatible blood cell antigens. Most of these antigens generally have been found accidentally as a consequence of a maternal-fetal incompatibility (as evidenced in hemolytic disease) or from crossmatching tests between potential blood donors and recipients.

The Rh blood group was found during experiments by Landsteiner and Wiener using rhesus monkey blood antiserum. This antiserum agglutinates 85% of white Americans' red blood cells, and they are, therefore, called Rh positive. The 15% or so individuals whose red cells are not agglutinated (and thus do not have the so-called Rh antigens) are Rh negative. The Rh-negative women will form anti-Rh in response to accidental transfusion of Rh blood cells or in response to pregnancy with Rh-positive infants. The red cells cross the placenta into the maternal circulation. It is thought that this occurs at the time of delivery, when the placenta is torn loose. With successive pregnancies, and sensitizations, the Rh-negative mother forms higher titers of anti-Rh antibody, which when transferred across the placenta causes the hemolytic anemia and full-blown syndrome of erythroblastosis fetalis.

About 10% of all infants are "at risk" for developing erythroblastosis secondary to Rh incompatibility (15% of women are Rh negative, and of these 85% will marry Rh-positive men). In turn, in only about one third of such matings, the father will be homozygous (RhRh), in which case all the offspring will be at risk. The number of infants affected by Rh incompatibility, however, is only about 1% to 2% of all newborns. There may be variations in susceptibility to sensitization or in the ability to form antibodies in Rh-negative women, which further reduces the risk of erythroblastosis for their offspring. If the father's Rh genotype has been determined and he is heterozygous (Rhrh), the risk is that about half of the children will receive the Rh-negative gene, and half, therefore, will be at risk. If the Rh-positive father's genotype is not known, the risk for each succeeding child to be Rh positive will be in the range of 70% or so. These probabilities may be of some help in advising the family with an Rh problem.

Hemolytic disease can also occur following other forms of blood incompatibility reactions (ABO, Kell). These incompatibilities must be recognized, and fortunately most blood banks now detect them. For the most part, however, the great toll of infants with kernicteric brain damage, deafness, and cerebral palsy has been due primarily to the Rh problem. We will discuss in our final chapter the new advances in immunization of the mother, which, one hopes, will prevent the sequelae of Rh hemolytic disease.

DISEASE AND BLOOD GROUPING

There is apparently an increased risk of gastric cancer in individuals with blood group A. This observation has been made by so many investigators that it may prove to be valid. A similar association of susceptibility has been documented

statistically with group O persons and duodenal ulcers. Other diseases and blood groups have been linked, but without strongly supportive statistical evidence.

Typing and histocompatibility problems in transplantation of organs

Proof of the individuality of man is convincingly expressed by the phenomenon of graft rejection. Generally, transplants of organs or tissues are not successful without the aid of immunosuppressive drugs. (The obvious exception to this generalization arises when the donor and the recipient of the graft are monozygotic twins.) The transplanted organ acts as a foreign antigen to the individual receiving the transplant, antibodies to the transplant are produced, and in a matter of days or weeks the skin, kidney, or other tissue is rejected. (Drugs, such as 6-mercaptopurine or its analogue, azathioprine, inhibit the antibody production, and thereby suppress the rejection process.) The antigens, which we believe to be structurally similar to lipoproteins, are present in a wide variety of tissue cells. The transplantation antigens, in turn, are controlled by a number of transplantation or histocompatibility genes. They apparently act according to a dominant hereditary pattern similar to the red blood cell group systems. A relationship exists between these tissue transplantation antigens (or histocompatibility factors) and leukocyte antigens. Thus, close compatibility of the organ donor and the recipient may be correlated fairly closely with the survival of the transplant. Typing of leukocytes (white blood cells), utilizing similar batteries of antisera as in red blood cell typing, may prove to be of great significance in the burgeoning field of transplantation.

Thus far, one leukocyte antigen system has been recognized (primarily utilizing the sera of multiparous women), and accurate white blood cell typing of individuals as a practical laboratory procedure is almost at hand. Interestingly enough, the first leukocyte antigen, recognized about 10 years ago, was called "Mac"; but a standardized (and more "scientific") nomenclature of white blood cell antigens is currently being established.

Another test or parameter of histocompatibility that is presently utilized in selection of transplant donors is the mixed leukocyte culture. We touched briefly on this procedure in Chapter 2 when we discussed the stimulation of lymphocytes and their transformation by mitogenic agents. The same antigenic variations between individuals that can be detected by graft rejections and leukocyte typings can be identified by the degree of blastlike transformation of lymphocytes in culture. Simply, when the white blood cells of two unrelated individuals are mixed and cultured in vitro for several days, the cells stimulate each other to enlarge and divide. The degree of transformation in the culture is apparently related to the degree of antigenic similarity between the individuals. The mixed lymphocyte culture of monozygotic twins shows no, or very little, such mitotic stimulation; and related individuals show comparatively less activity than completely unrelated individuals. These individual-specific antigens in the lymphocytes seem to corre-

late with the tissue-rejection antigens on the transplanted organs. The test is useful for prediction of the fate of these grafts.

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Chapter 11

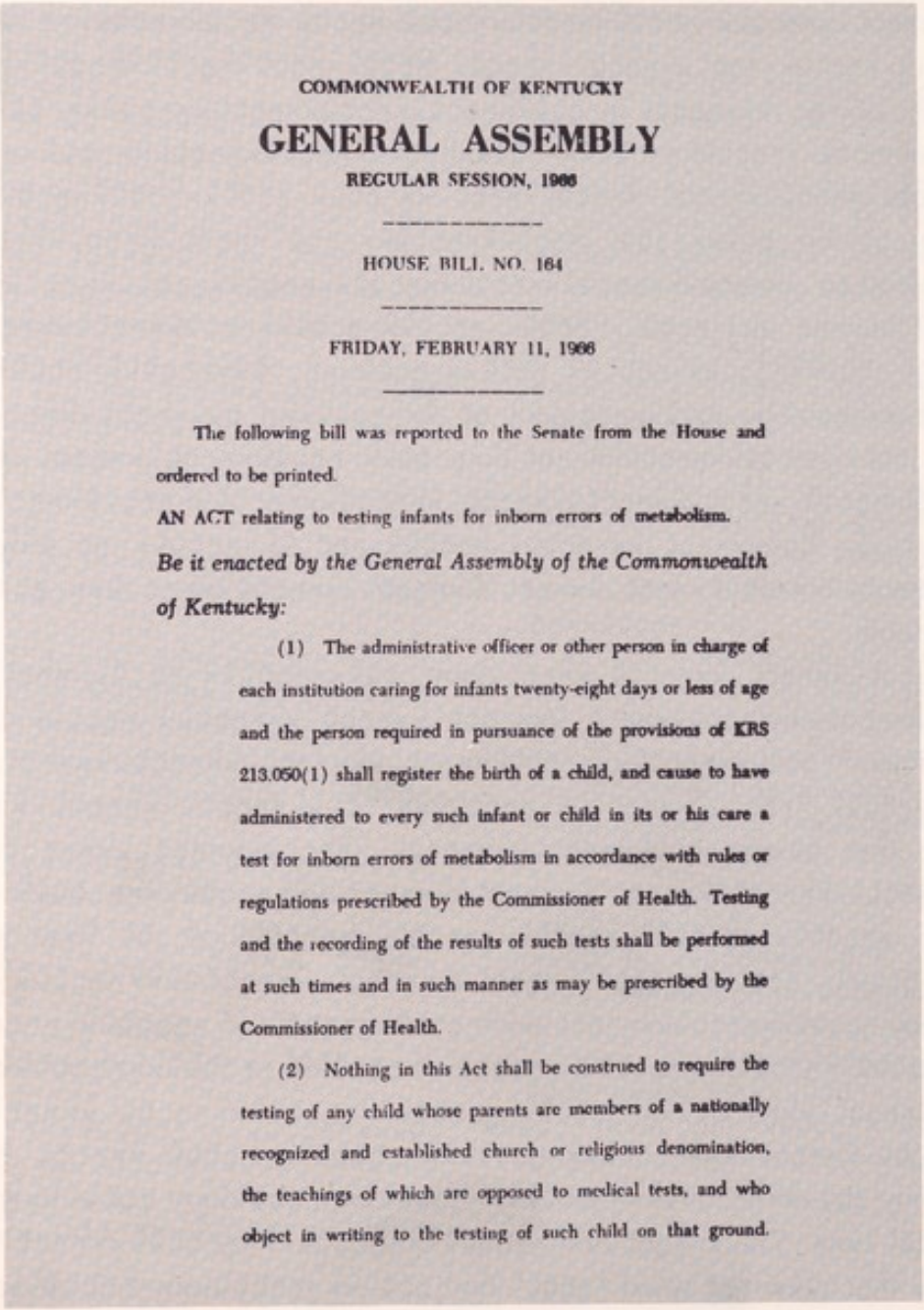
The inborn errors

The exact incidence of mental retardation due to the inborn errors of metabolism is not known, but a good estimate would place the incidence at approximately 5% of the retardates in institutions. (For comparison's sake, Down's syndrome makes up roughly 10% of mentally retarded individuals, and central nervous system developmental defects make up about 25%). Many of the diseases caused by inborn errors, like phenylketonuria and maple syrup urine disease, generally lead to profound mental retardation and institutionalization. Others, like sickle cell anemia and cystic fibrosis, are not related to mental retardation but mean long, chronic, spiritually as well as financially bankrupting illnesses to the affected families. The exciting aspect of the so-called metabolic diseases is that with our increased understanding of their basic biochemical, genetic, and pathogenic mechanisms, we are now frequently in a position both to prevent recurrence of these tragic illnesses in individual families and to improve the prognosis for infants already born with such defects. Certainly, several of the diseases now seem to be treatable.

The term "inborn errors of metabolism" was coined by Sir Archibald Garrod, early in the twentieth century, to describe a group of familial diseases (alkaptonuria, albinism, pentosuria, and cystinuria) that are characterized by specific enzyme defects. The absence or deficiency of a specific enzyme leads to a block in the normal metabolic pathways. The essential defect is at the genetic level. This defect is an impaired genetic mechanism leading to the enzymatic abnormality. The relationship has been called the "one gene, one enzyme" theory. The concept of these hereditary biochemical defects was proposed many years before enzymes were even crystallized and their protein structure identified. In fact, none of the enzymes involved in the inherited biochemical defects such as phenylketonuria or galactosemia, as well as the group originally described by Garrod, has yet been crystallized and examined directly. At present we can only demonstrate their activity (or lack of activity) indirectly by certain biochemical tests. The nature of Garrod's studies is even more remarkable when we realize that even the word "gene" had not yet really been defined at the time of his work.

To cite but one example, Garrod described the hereditary defect known as

alkaptonuria. The metabolism of tyrosine involves its degradation in successive steps. In alkaptonuria, the metabolic pathway is blocked by the production of a substance called alkapton (or homogentisic acid). The missing enzyme, necessary for breakdown of the homogentisic acid, is apparently homogentisic oxidase, an enzyme usually manufactured in the liver. Because of the block, the homogentisic acid piles up in the blood and tissues. Excreted in large quantities in the urine, it causes a blackish discoloration on standing for several hours; deposited in some of the cartilaginous structures of the body, it eventually causes a blackish pigmentation (ochronosis), very often involving the ear and nasal cartilages. (We wonder



COMMONWEALTH OF KENTUCKY

GENERAL ASSEMBLY

REGULAR SESSION, 1966

HOUSE BILL NO. 164

FRIDAY, FEBRUARY 11, 1966

The following bill was reported to the Senate from the House and ordered to be printed.

AN ACT relating to testing infants for inborn errors of metabolism.

Be it enacted by the General Assembly of the Commonwealth of Kentucky:

(1) The administrative officer or other person in charge of each institution caring for infants twenty-eight days or less of age and the person required in pursuance of the provisions of KRS 213.050(1) shall register the birth of a child, and cause to have administered to every such infant or child in its or his care a test for inborn errors of metabolism in accordance with rules or regulations prescribed by the Commissioner of Health. Testing and the recording of the results of such tests shall be performed at such times and in such manner as may be prescribed by the Commissioner of Health.

(2) Nothing in this Act shall be construed to require the testing of any child whose parents are members of a nationally recognized and established church or religious denomination, the teachings of which are opposed to medical tests, and who object in writing to the testing of such child on that ground.

Fig. 11-1. Reproduction of the 1966 law relating to the detection of phenylketonuria in the newborn in the state of Kentucky.

if those people with the "tips of their noses black," described by Paré early in the seventeenth century, were, in truth, alkaptonurics.) Except for one effect, chronic arthritis, which generally starts after middle age and is probably caused by deposits of the pigment in the connected tissues, alkaptonuria is a relatively benign disease. It does, however, serve as a good example for the study of the other inborn errors of metabolism.

The list of metabolic diseases has been growing at a rapid pace—about thirty inborn errors of amino acid metabolism alone now have been described. The clinician has to face an ever increasingly difficult (and almost overwhelming) job of keeping up with the almost daily discoveries of new diseases (and of biochemical errors for which there are yet no clinically described diseases). The physician also has increasing responsibility (in many states under legislative duress) of making an early diagnosis of these diseases, and possibly avoiding the damaging sequelae (Fig. 11-1). Treatment of a biochemical abnormality, rather than a clinically diagnosed disease, is now almost obligatory in the care of phenylketonuria. In the near future, treatment should be forthcoming for many other diseases listed in this chapter.

Early diagnosis depends upon the taking of a family history, utilizing screening tests for the abnormal accumulations of metabolic products in affected individuals, and, occasionally, finding certain characteristic physical abnormalities. Early recognition of phenylketonuria, galactosemia, and cretinism is obviously vital. Currently, 10% of the admissions to pediatrics services throughout the United States are children with genetic defects of many different kinds. It is obvious that a great part of future medical practice will consist of the management of these children with hereditary biochemical errors and of counseling their families. Comprehensive discussion of all these diseases is beyond the means and intent of this book. We would like to confine ourselves to the problems and questions more likely than others to come to the practicing physician's office. In our description of phenylketonuria, we will attempt to comment on the genetic aspects, therapeutic approaches, counseling considerations, and usual philosophy that can guide the clinician in a general way through experiences with this and other types of metabolic disorders. Some of the other more commonly encountered diseases will be summarized in Table 11-1. A host of other allied diseases, some fairly common and some very esoteric, can be found in the references at the end of the chapter.

PHENYLKETONURIA—THE DEFECT

Garrod noted that alkaptonuria involves a specific block in the metabolic pathway of tyrosine. Another essential and very common dietary amino acid, phenylalanine, itself is degraded normally to tyrosine as part of the protein metabolic cycle in man. The necessary catalyst for one of the steps is the hepatic enzyme phenylalanine hydroxylase, and, in individuals with phenylketonuria, this enzyme is absent. The failure of proper conversion of phenylalanine to tyrosine re-

Text continued on p. 164.

Table 11-1. Some inborn errors of metabolism

Disease	*Type of inheritance*	*Metabolic or biochemical defect*
Adrenogenital syndrome	Autosomal-recessive (80% are female)	Deficiency of 21-hydroxylase in adrenal cortex; failure of synthesis of hydrocortisone
Afibrinogenemia	Autosomal-recessive	Failure in fibrinogen synthesis
Agammaglobulinemia	Sex-linked recessive	Absence of gamma globulin
Albinism	Autosomal-recessive	Block in conversion of tyrosine to dopa (melanin synthesis); absence of tyrosinase
Cystic fibrosis	Autosomal-recessive	1. Abnormality of exocrine glands 2. Sweat has high concentration of sodium chloride
Cystinosis (Fanconi syndrome)	Autosomal-recessive	Defect in renal transport mechanism, involving many amino acids
Cystinuria	Autosomal-recessive	Renal transplant defect involving reabsorption of cystine, lysine, arginine, and ornithine
Diabetes insipidus	Autosomal-dominant	Deficiency of excretion of vasopressin by pituitary gland
Galactosemia	Autosomal-recessive (heterozygote can be detected)	Failure of conversion of galactose-1-phosphate to glucose-1-phosphate (missing enzyme is galactose-1-phosphate uridyl transferase)
Gargoylism (Hurler's syndrome)	1. Autosomal-recessive 2. Sex-linked in some cases	1. Disorder of mucopolysaccharide metabolism 2. Excess chondroitin sulfate B and heparitin sulfate in urine
Gaucher's (infantile form)	Autosomal-recessive	Defect in lipid metabolism leading to accumulation of cerebroside in spleen and central nervous system
Gilbert's disease (familial nonhemolytic jaundice)	Dominant with incomplete penetrance	Deficiency of glucuronyl transferase in liver

Incidence in population (United States)	*Primary symptoms*	*Therapy*
1/25,000	Progressive virilization	1. Hydrocortisone 2. "Salt-losers" need desoxycorticosterone acetate 3. Surgical correction of abnormal genitalia
Rare, about 100 cases reported	Hemorrhage	Transfusions
Rare	Repeated infections	Gamma globulin
1/10,000	1. Lack of skin, hair pigment 2. Eye defects	1. Avoidance of sunlight 2. Ophthalmological care
1/2,500-1/4,000 (1/25 carrier frequency)	1. Meconium ileus in newborn 2. Celiac syndrome 3. Pulmonary disease 4. Stunting of growth	1. Antibiotics 2. Pancreatin 3. Inhalation therapy
Not known	1. Rickets 2. Chronic acidosis 3. Dwarfism 4. Glucosuria 5. Cystine crystals in reticuloendothelial system, kidneys, etc.	1. Vitamin D 2. Calcium and phosphate in diet 3. ? penicillamine
1/100,000	Renal calculi	Alkalinization of urine to prevent formation of renal stones
1/10,000-1/20,000	Polydypsia, polyuria	Posterior pituitary extract by nasal insufflation or injection
1/25,000 births	1. Failure to thrive 2. Mental and motor retardation 3. Cataracts 4. Jaundice 5. Some *perfectly normal* individuals described	Low galactose diet may prevent symptoms and even reverse some if instituted early
1-10,000/20,000 births; about 150 families described	1. Dwarfing 2. Progressive mental deterioration 3. Corneal clouding 4. Enlarged liver and spleen 5. Early death	None
Rare	1. Cachexia 2. Splenomegaly 3. Death usually within two years	Splenectomy occasionally helps for a short time
Not known	Jaundice with only midly increased bilirubin levels	None required

(Continued)

Table 11-1. Some inborn errors of metabolism—cont'd

Disease	*Type of inheritance*	*Metabolic or biochemical defect*
Hartnup disease	Autosomal-recessive	1. Defective transport of tryptophan in renal tubules 2. Block in nicotinamide formation
Histidinemia	Autosomal-recessive	1. Excessive histidine in blood and urine 2. Deficiency in histidase enzyme 3. Positive ferric chloride test
Homocystinuria	Autosomal-recessive	1. Absence of cystathione synthesase enzyme in liver and brain 2. Increased homocystinuria in plasma and urine
Lesch-Nyhan syndrome	Sex-linked recessive	Disorder of uric acid metabolism
Lowe's syndrome (oculocerebrorenal syndrome)	Sex-linked recessive	Aminoaciduria Renal tubular abnormality
Marfan's syndrome (arachnodactyly)	Dominant with variable expression	Abnormality of collagen fibers
Maple syrup urine disease	Autosomal-recessive	Defect in metabolism of branched-chain amino acids
McArdle's syndrome	Autosomal-recessive	Absence of muscle phosphorylase
Niemann-Pick disease	Recessive	Disturbance in lipid metabolism leading to excessive sphingomyelin in reticuloendothelial cells and central nervous system
Pseudohypoparathyroidism	Autosomal-dominant	Defect in renal tubular response to parathyroid gland
Renal glycosuria	Autosomal-dominant	Defect in renal transplant mechanism for glucose, with glucose spilling into urine
Sickle cell anemia	Autosomal-recessive	Sickle hemoglobin causes shortened red cell life-span ("sickling")

Incidence in population (United States)	*Primary symptoms*	*Therapy*
About a dozen families described	1. Photosensitivity 2. Skin rash 3. Cerebellar ataxia 4. Aminoaciduria	1. Administration of nicotinamide 2. Avoid exposure to sunlight 3. Low amino acid diet
Very rare; only a score or so cases reported	1. Psychomotor retardation 2. Speech defect	1. ? Low histidine diet 2. Speech therapy
Rare, but frequency as biochemical cause of mental retardation is second only to PKU	1. Deafness 2. Mental retardation	? High cystine–low methionine diet
Rare	1. Hyperuricemia 2. Mental retardation 3. Self-destructive biting	None
Very rare; only 22 cases reported thus far	1. Cataracts 2. Mental and growth retardation 3. Rickets 4. Osteoporosis	None (rickets may improve with vitamin D)
2/100,000	1. Ocular defects, ectopia lentis 2. Dissecting aneurysms 3. Tall, thin individuals with long tapering "spider" fingers	Surgical correction of defects
Very rare; a handful of families described	1. Onset in early infancy 2. Cerebral symptoms and early death 3. Maple sugar odor in urine	Diets low in branched-chain amino acids; good results apparently in the few individuals followed
Rare	Muscle weakness	Glucagon injections
Rare; 50% of patients are Jewish	1. Blindness 2. Progressive neurologic deterioration 3. Hepatomegaly	None; fatal in early childhood
Rare; 50 or so cases reported	1. Hypocalcemia 2. Hyperphosphaturia 3. Short stature 4. Short digits 5. Cataracts 6. Mental retardation	Vitamin D
Rare	1. Excretion of glucose in urine, even with normal blood sugar 2. No symptoms	Benign No therapy indicated
1. 0.25% of Negroes 2. 8% of Negroes have trait (A/S)	1. Chronic anemia 2. Cardiac, renal, cerebral complications	1. Symptomatic therapy 2. Life-span shortened considerably

(Continued)

Table 11-1. Some inborn errors of metabolism—cont'd

Disease	*Type of inheritance*	*Metabolic or biochemical defect*
Tay-Sachs (amaurotic family idiocy)	Autosomal-recessive	Defect in synthesis of gangliosides
Thalassemia	Homozygotes have thalassemia *major;* heterozygotes show thalassemia *minor*	Block in synthesis of adult hemoglobin leads to defective red blood cells
Vitamin D–resistant rickets	Sex-linked dominant	Renal tubular defect in reabsorption of phosphate
von Gierke's (glycogen storage) disease	Autosomal-recessive	Block in metabolism of glycogen back to glucose (glucose-6-phosphatase deficiency)
Wilson's disease	Autosomal-recessive	Disturbance in copper metabolism; deficiency of plasma protein ceruloplasmin

sults in accumulation of phenylalanine in the blood (and spinal fluid) and the excretion of some of its degradative metabolites, such as phenylpyruvic acid and other phenylketone products, in the urine. Thus, instead of a normal phenylalanine level of 1 mg. per 100 ml., phenylketonurics may have levels of 10 to 60 mg. per 100 ml. Instead of the minimal amounts of phenylpyruvic acid usually found in the urine, phenylalanine and the other derivatives are found in markedly increased quantities. It is important to recognize that the metabolites themselves are not necessarily abnormal, but that the amount of accumulation in the various tissues of the body is abnormal.

Genetic aspect

Garrod suspected that alkaptonuria is inherited as a recessive trait because in a good number of the families there were two or more siblings affected, and marriages between first cousins were commonly found among the pedigrees. Phenylketonuria, like alkaptonuria and a great number of all the diseases involving inborn errors, is recessively inherited. The pedigree of one of the families coming to our clinic shows clearly the recessive nature of phenylketonuria (Fig. 11-2). We demonstrated in Chapter 4 that the carrier of a recessive gene (or heterozygote) will have affected children only if he or she marries an individual who is also a carrier of that gene. The number of carriers of the PKU gene in the population is estimated at about one in seventy. Ordinarily, therefore, the risk that a

Incidence in population (United States)	*Primary symptoms*	*Therapy*
12/100,000 in Jews 0.2/100,000 in non-Jews	1. Blindness ("cherry red spot") 2. Progressive neurologic deterioration 3. Early death	None
1. 1/2,500 of Italians in United States 2. 1/25 of Italians have minor form	1. Chronic anemia Hemosiderosis	1. Frequent transfusions 2. Early death because of complications secondary to frequent blood transfusions
1/20,000	1. Hypophosphatemia 2. Rickets 3. Craniostenosis	Vitamin D
1/20,000 births	1. Enlarged liver 2. Hypoglucosemia 3. Ketosis 4. Convulsions, coma	1. High protein diet 2. Treat acidosis and hypoglucosemia 3. Usually early death
1/25,000	1. Cirrhosis 2. Kayser-Fleischer ring of cornea 3. Renal calculi 4. Neurologic manifestations	1. Penicillamine (copper chelating agent) 2. Poor prognosis

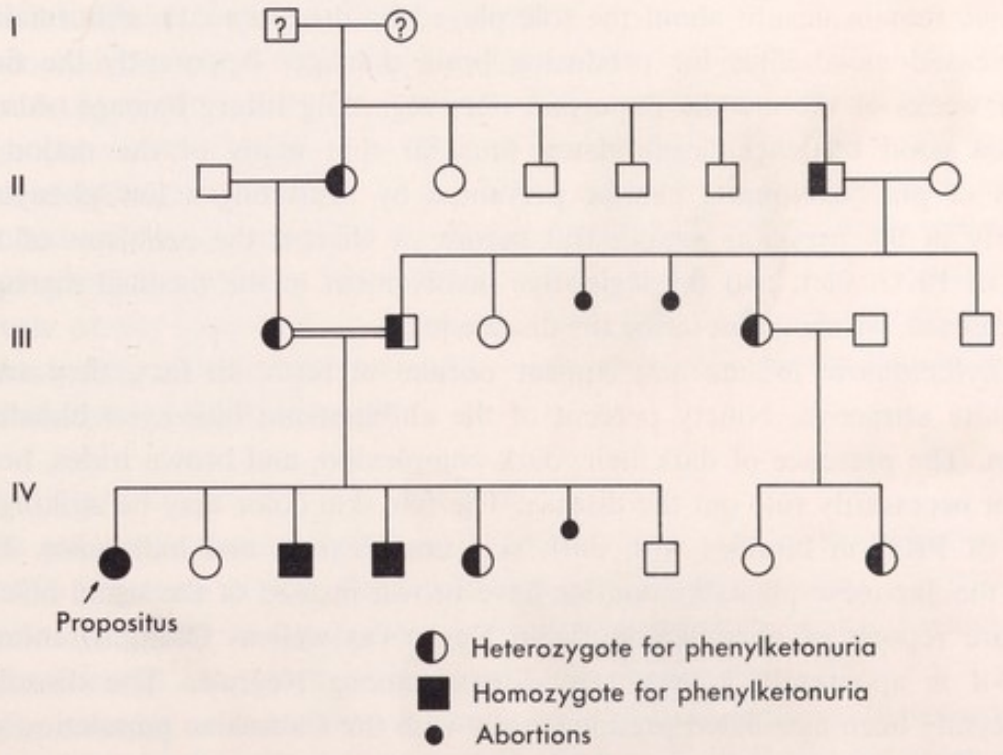


Fig. 11-2. Pedigree of a family showing the recessive inheritance pattern of phenylketonuria. Note the consanguinity in this family.

heterozygote would mate with another heterozygote is one in 4,900 (70 × 70). The risk would be much higher than this figure suggests if the carrier marries a close relative (as we have discussed previously in mathematical terms). For example, if the heterozygote marries a second cousin, the risk of having married a a person with the same abnormal PKU gene would now be in the range of one in 2,240 (70 × 32). Thus, in the individual family, the risk of defective children is increased by as much as 50% if there is a second cousin marriage involved.

In the family described in the aforementioned pedigree, three out of six liveborn children have the homozygous phenotype of phenylketonuria. Two are in a state training school, two are apparently normal, and one is a heterozygote. Detection of the heterozygote carrier of the PKU gene will be discussed at greater length later. Of course, a hypothetic family could have, on the average, the ratio of one (normal): two (carrier): one (affected) in the offspring of two heterozygotes, but we only rarely meet hypothetic families in our clinic.

Disease characteristics

Phenylketonuria is a rare disease, the incidence in our population being one in 10 to 20,000 births. About 1% of mental retardates who are in institutions have the disease, so that the relationship to mental retardation seems at first glance fairly obvious. The same biochemical abnormality, with high levels of phenylalanine in the blood, has also been described, however, in individuals with normal intelligence. In fact, some of these people have above-average intellects. PKU, therefore, may not represent an "all-or-none" phenomenon in regard to mental deficiency. Even though PKU is a model for the study of the inborn errors, we remain unsure about the role played by the enzymatic abnormality and the increased metabolites for producing brain damage. Apparently the first few days or weeks of life are the important ones regarding future damage. Also there has been good evidence accumulated thus far that many of the major consequences of phenylketonuria can be prevented by instituting a low phenylalanine diet early in the neonatal period. But before we discuss the problems of the detection of PKU, diet, and the legislative involvement in the medical management of this disease, we should describe the disease itself.

Phenylketonuric infants may appear normal at birth. In fact, they are most often quite attractive. Ninety percent of the children are blue-eyed blondes with fair skin. The presence of dark hair, dark complexion, and brown irides, however, does not necessarily rule out the disease. The fair skin color may be strikingly suggestive of PKU in families with dark skin complexions and hair color. For example, the Japanese phenylketonurics have brown instead of the usual black hair. There are reports of phenylketonuria in Negro (as well as Oriental) infants, although it is apparently a very rare disease among Negroes. The disorder has until recently been associated predominantly with the Caucasian population groups. The fair skin and hair color may be related to an associated defect in the melanin pigment production caused by the accumulation of toxic metabolites of phenyl-

alanine. This causative effect is suggested by a change in skin color that occurs very frequently after dietary treatment has been instituted in the infants.

The untreated PKU infants fail to thrive, and most often they will fall in the lowest percentile groups for weight and height. Chronic vomiting, unusual irritability, and an atopic type of eczema are very common in infancy. Anyone who has examined a PKU child will recall distinctly the "mousey" or musty odor. This characteristic smell, probably related to the excretion of the phenylacetic acid metabolite in the urine, can be a helpful diagnostic clue for the examining physician. The children very often have microcephaly; neurological symptoms of one sort or another are seen very commonly. Bizarre hand posturing, tremors, athetotic movements, sometimes frank spasticity (with the frequent incorrect diagnosis of cerebral palsy), and occasionally almost autistic behavior may be part of the picture presented to the physician. Epileptic seizures occur in perhaps 25% of the patients. Abnormalities as seen on the encephalogram, on the other hand, are almost universally present. These include a variety of electroencephalographic abnormalities, including hypsarhythmia.

Of course, mental deficiency is the most common characteristic of phenylketonuria. Mental retardation becomes obvious when the children fail to match the usual norms for motor and, later, language milestones of development. Generally, the retardation is ultimately so severe that most of the individuals have to be institutionalized. In one large group studied, about 40% never learned to walk, and 50% never acquired any speech. The same investigator found that the majority of his group of phenylketonurics did not show intellectual progress beyond a mental age of 2 years. This group of children had had no special dietary regimen. The degree of severity of the mental deficiency, however, did not correlate with the levels of phenylalanine found in the serum.

It must be reemphasized that many individuals have now been found—generally through the ferric chloride screening tests and the other newer screening procedures of siblings of patients, or on routine survey—who are perfectly normal in intellectual and neurological functions. These individuals have been referred to as atypical phenylketonurics. Their phenylalanine levels are frequently elevated to the levels of the typical phenylketonurics. We will discuss the problem of these individuals with elevated phenylalanine levels who are perfectly normal intellectually a little later on in the chapter.

Tests

The phenylketonuric infant has a high blood level of phenylalanine soon after birth. The diagnosis of the disorder is based on the finding that phenylalanine in elevated amounts is found in the serum and in the keto acid derivatives in the urine later on in infancy. Since Fölling originally described PKU (in a group of mentally retarded individuals) as characterized by having the substance in the urine that reacted with ferric chloride, forming a green color, the examination of urine with that reagent has been a standard test for the disorder. The phenyl-

pyruvic acid in the urine generally will not be detectable in the urine of affected children for the first few weeks of life, so that accurate testing can be done only at a month of age or later. With normal feedings the affected baby's serum levels of phenylalanine will be markedly elevated to values of 20 mg. per 100 ml. or so within the first week of life. Thus, the most effective way of testing would be by determination of phenylalanine blood levels rather than by relying on urinary examination.

Several methods are now available for the rapid and relatively inexpensive determination of these levels. The Guthrie test utilizes a bacterial inhibition assay technique; the test devised by McCaman and Robins involves a more exact fluorometric determination. (Descriptions of both these procedures will be found in the references at the end of the chapter.)

The immature enzyme systems in some infants, especially in prematures, may lead to "false positives." These premature babies will often have moderately elevated phenylalanine levels in the first few days of life, but these gradually decrease to normal levels.

It is obvious that laboratory documentation is needed to establish the diagnosis of many of the metabolic errors. This involves quantitative analyses of various biologic fluids (plasma, urine, sweat) for amino acids, abnormal lipids, adrenal steroids, etc., which are beyond the scope of the practicing physician's examination. He can keep a bottle of 5% ferric chloride on a shelf under the examining table (or more practically utilize the Phenistix tests now available) and test for phenylketonuria and histidinemia, but most other examinations will have to be done by a reliable laboratory. In addition to PKU and histidinemia, the multiple screening tests (utilizing paper chromatography and other techniques) are now practical for detecting galactosemia, agammaglobulinemia, Wilson's disease, maple syrup urine disease, and a growing list of other metabolic diseases.

Diet

When does the damage occur in phenylketonuria? Since the enzyme phenylalanine hydroxylase is normally not active before birth, it is believed that the PKU infant does not sustain brain damage in utero. The insult apparently takes place during the development of the brain in early infancy. There is current statistical evidence that if affected children are treated with a low phenylalanine diet during the early neonatal period, the child has a good chance for normal mental development—yet, the exact nature of the cause of the brain pathology in PKU is still unknown.

One of the most hopeful, and now most controversial, areas of interest in the metabolic diseases has been that of treatment, especially treatment by a special diet. Since the defective enzyme in these diseases is intracellular, one cannot hope to administer the enzyme, even if it were able to be synthesized, systemically (as we treat diabetes mellitus with an insulin injection). Instead, there is an attempt to eliminate from the diet certain foods containing the substance that ac-

cumulates excessively as a result of the block we described earlier. The prime example of the potential success of such dietary management is PKU, in which diets low in phenylalanine are used. During infancy, the child is placed on a diet that replaces milk with a protein hydrolysate. Milk, we know, contains high amounts of phenylalanine.

There is available evidence that a low phenylalanine diet does have an effect on reducing the incidence of mental deficiency among children with PKU. In a good number of cases the diet has been beneficial, especially when it is started in the first few months of life. If treatment is started later, the results as far as intelligence is concerned are not consistent. Some of the problems raised by these inconsistent results are the following:

1. We do not actually know whether the cause of damage to the brain is the phenylalanine or the metabolites, and we do not know if any of these substances actually cause brain damage.
2. The screening programs are detecting more and more normal people with PKU.
3. The low phenylalanine diet may cause death if improperly supervised, because of the severe deprivation of this essential amino acid.
4. The laws inacted by a majority of the states are now making testing, and, therefore, therapy a compulsory matter and have introduced the concept into many people's thinking that a child with the disease can eat his way into mental and physical normality.

DETECTION OF THE CARRIER

We have emphasized the significance of autosomal-recessive inheritance to the parents. In most cases the parents are heterozygotes for the abnormal trait. The *healthy* siblings (or future healthy children) will have a 66 ⅔% risk for being a carrier. Although, in man, diseases and anomalies caused by one-gene inheritance are primarily dominant traits (see Chapter 5), Table 11-1 indicates that a majority of the inborn errors are recessive in nature.

The question we are most often asked is whether the siblings are indeed heterozygous for the abnormal gene. In phenylketonuria, heterozygosity can be determined fairly accurately. A "loading dose" of phenylalanine is administered to the individual orally, and plasma levels of the amino acid are measured. The heterozygous carrier will often have a plasma level about two or three times the normal control values.

The same sort of loading test (this time utilizing galactose) can differentiate the carrier of the galactosemia gene. The sweat electrolytes may frequently be elevated in parents and siblings of children with cystic fibrosis, but the overlap of these measures with those of normals is too great to make the test useful as of now.

Heterozygosity for the sickle hemoglobin gene can be detected by hemoglobin electrophoretic patterns. The individuals with sickle cell trait generally show about

40% hemoglobin S and 60% hemoglobin A. Several other recessively inherited diseases will soon be detected with accuracy in the heterozygote when our techniques are improved.

Siblings of children with phenylketonuria (and galactosemia) should be tested. It would seem reasonable that their prospective marriage partners should also be tested. Even if they do marry with the knowledge that they are carriers, at least their family physician will be alerted to the possibilities that a disorder can occur. Detection can thereby be afforded *early* in the life of their offspring.

COUNSELING CONSIDERATIONS

Although the first four inborn errors described by Garrod, and many of the other inborn errors since described, are relatively benign diseases that do not generally interfere with a normal life-span or impose serious consequences, most do create specific problems for the individual family. The genetic counselor not only must be prepared to discuss the parents' chances for having another child with the same disease (and the chances of other individuals in the family for being carriers of the anomaly as a recessive trait) but also must be aware of other problems, such as where to refer the child for therapy or how to help the parents avoid inaccurate beliefs about their child's disease. For example, we could help them avoid the "tobacco road" folklore that has grown up about albinism—with the impression, at least to most individuals and many physicians, that mental retardation or simplemindedness is a common finding among individuals with albinism. We like to reassure our families with the fact that there is no reason to believe that there should be any lack of normal intelligence in their children who have albinism. We never fail to mention the names of famous men who were albinos. These names include Reverend Spooner, the famous English clergyman and scholar, whose famous slips of the tongue gave rise to "spoonerism." His loquacious success serves as an example that mental retardation does not necessarily go along with albinism. Another misconception is that albinos have pink eyes. Pink eyes (or pink irides and pupillary reflexes) are found in albino mice and rats, and in some young infants—but in mature human albinos the pupil is black and the iris blue-gray. We do, however, emphasize the importance of ophthalmological examination because of the high frequency of photophobia, poor visual acuity, nystagmus, and strabismus among albinos. Occasionally, congenital defects like aniridia and atrophia of the disc do cause blindness, but certainly there is no need to put an albino child with only minimal loss of visual acuity into a school for the blind—as was recommended to one of our families by a well-meaning but misinformed physician.

Parents of children with a recessive abnormality should be told about the risks involved. Each succeeding child runs a 25% risk of having the same disorder and a 50% risk of being a carrier like the parents. It is important in this regard to emphasize that both parents are heterozygotes, and to explain this in simple terms. For example, the parents of a child with cystic fibrosis should be

made aware of the increased risks that each one of their healthy children may be a heterozygote. This risk for each normal or healthy child is 50% when we cannot tell the carrier from the completely normal children. The parents should also know the increased risk of such carrier-children's marrying consanguineously. For example, in cystic fibrosis, in which the carrier rate is especially high for such a lethal or harmful gene (it is about one in twenty-five in the population), the heterozygous sibling of a child with the disease runs a 4% risk for marrying another heterozygote *even if he does not choose a relative*. The chances are somewhat more favorable for PKU and most of the other rarer diseases for the carriers of these mutant genes marrying a person who is not a heterozygote—but again, there still is the significant risk that must be explained to the parents.

It is obvious that determination of the heterozygote is a crucial factor. Unfortunately, the heterozygote can be determined with considerable accuracy only in phenylketonuria and a few other diseases, such as sickle cell disease and thalassemia. In jest, it has been suggested that heterozygous carriers be identified with a forehead tattoo (somewhat like the "scarlet letter") to warn potential marriage partners—we are not sure that this measure would work satisfactorily. Individual families are the concern in the clinic or in the physician's office, and we can only advise particular husbands and wives who are suspected carriers about their increased chances for having affected children. We would certainly suggest adoption for such families. It seems to us that the giving of advice about whether to have additional children, or not to attempt another pregnancy, is the prerogative and the decision of the counselor. If he is a family physician who has close rapport with the couple, he can go beyond merely presenting the hard facts and can offer advice about their decision. The counselor who sees the husband and wife only for an hour or so in his office generally will not wish to become directly involved in this family's decisions about future children, but will merely present the available data. Whatever the situation, counselors giving advice about family planning should be aware of religious considerations. Further advice from clergymen can be especially helpful.

We can pick one disease, cystic fibrosis, to provide a guide for additional counseling considerations about inborn errors. Cystic fibrosis is one of the most serious diseases encountered in genetic counseling. Its lethality, the expense involved in its treatment, and its punishing effect on the family should be grave concerns for any counselor. The prospect for salvaging a baby or child is now brighter, but such a prospect is gloomy when one considers the possibilities of economic and spiritual ruin to a family. The counselor, be he family physician or specialist, should be very much aware of the nonmedical side effects resulting from a child's having cystic fibrosis.

The treatment of cystic fibrosis is, of course, a medical responsibility. Some physicians may shirk this responsibility because of the emotional drain that comes from dealing with these families. In a sense, the physician's difficulties are like those encountered in dealing with the families who have leukemic children. He

has to measure hope judiciously, he has to provide realistic guidance, and he has to help promote family stability in the face of chronic crisis. This is an onerous task for any physician to consider. Some of these burdens are often shifted to the family. The counselor should be aware that children with cystic fibrosis require therapeutic regimens that are carried out by the parents at home. He should try to judge whether the parents are capable of taking on the responsibilities of life or death actions for their child.

The counselor should also be aware that the advice he gives to parents of children with cystic fibrosis may affect the entire life pattern of the family. Expense certainly changes parental living patterns, as does worry; but a child with a serious disease affects *all* family members. Normal expectations for the sick child's behavior are sometimes changed, to his and his sibling's detriment. As much as possible, the counselor should not encourage or support major alterations in the family's pattern of life, no matter how much he or the family feels sorry for the child. It is unfortunate to see a family who have added emotional problems to their other burdens.

A final point for the counselor to consider is what he should tell the child with cystic fibrosis. We personally think that, at the appropirate time, the counselor should be prepared to answer or help the parents answer the child's questions about his illness. Even very young children want to know what is happening to them. Lame answers given with the best of intentions will not allay further curiosity. Older children can even learn from our evasiveness not to trust us. This is hardly an ideal situation—especially when we expect some of these children to heed our advice when they live to become adults.

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Chapter 12

Genetics and cancer

Retinoblastoma is the most frequently occurring intraocular malignancy in childhood, but it is relatively rare (only about 100 cases are diagnosed each year in the United States). The diagnosis is made at an average age of 1 to 2 years—retinoblastoma occurring most often with no history or evidence of preexisting eye disease. This malignancy is now known to be hereditary. The affected children carry a particular single dominant gene, which causes its development. Retinoblastoma exemplifies the fact that some types of cancer, or at least a susceptibility to them, can be inherited. If the child with retinoblastoma has been born to normal parents, he probably represents a new mutational gene. The likelihood that a second child in the famly will be affected is very small—about the same as in any other family. However, if the child survives and reaches adulthood, he can expect that close to 50% of his own offspring will be affected. In this and similar instances, genetic counseling takes on great importance. This chapter will be concerned with the genetic factors causally related to retinoblastoma and other forms of malignancy, including leukemia, and with the counseling demands that such conditions entail.

LEUKEMIA

In spite of intensive effort, the etiology of human leukemia eludes us. However, our understanding of the possible causative factors has increased considerably in the past few years. Indeed, it now seems more than likely that the cause of leukemia in man will be related ultimately to a combination of factors, including genetic susceptibility, rather than to single etiologic agents such as exposure to radiation or a particular virus.

Genetic factors in leukemia

The significance of genetic factors as determinants for the development of leukemia has been tested for by the examination of large groups of identical twin pairs. Monozygotic (identical) twins develop from a single fertilized ovum, thus having a presumably identical genetic makeup. If the genetic determinants were more important than environmental factors, it would be expected that if one twin developed leukemia (or another type of cancer), the other might develop the same

malignancy, at the same place and of the same type. But the evidence thus far indicates that although the incidence of leukemia is somewhat higher in the identical twin group, it is not significantly high enough to implicate clearly hereditary factors as being a primary cause.

There are also a few reports of cases in which three or more children in one family have been affected by leukemia. These rare leukemia families are certainly highly selective, but they may represent more than just chance occurrences. The children in several of these families are the offspring of consanguineous marriages, strongly suggesting that at least *in these individuals* a recessive gene might be involved.

Although several recent studies indicate that the risk of cancer (and leukemia) for the siblings of leukemic children is statistically excessive, single hereditary factors probably play only a small part in the development of leukemia. Certainly, in counseling the family, the rarity of occurrence of leukemia in siblings of the affected child should be stressed.

Chromosomal abnormalities in leukemia

Leukemia, like the other malignancies, represents the unlimited and uncontrolled growth of cells and tissues that have become independent of the body's normal control mechanisms. Boveri, in 1914, first suggested that a break-

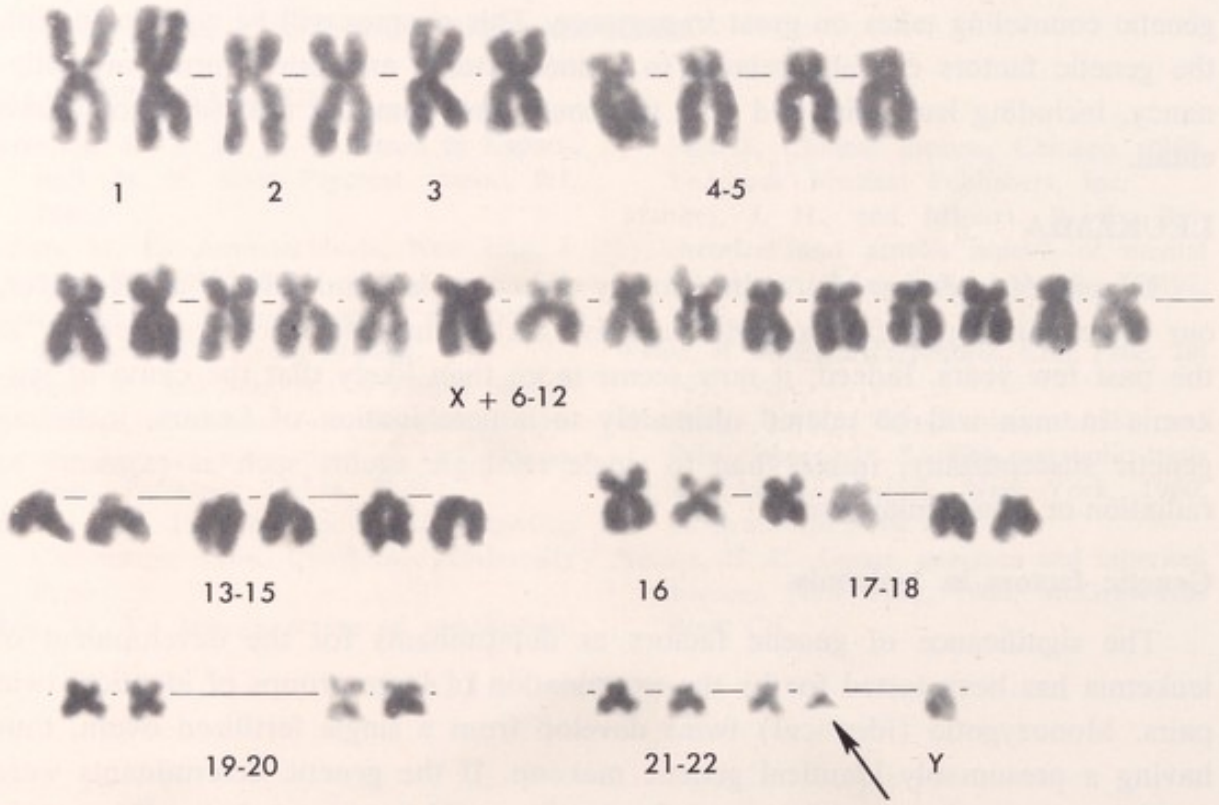

Fig. 12-1. Arrow indicates Ph¹ chromosome in a peripheral blood culture of a patient with chronic granulocytic leukemia.

down of mitotic control related to the devolpment of malignancy might lead to chromosomal abnormalities. Certainly the primary event in the pathogenesis of the leukemia may be a *somatic mutation,* which gives rise to a disturbance in normal cell division. The mitotic accident might then lead to a chromosomal rearrangement and ultimately to a transformed malignant cell.

Philadelphia (Ph^1) chromosome

The discovery of the Ph^1 chromosome was a milestone in research in the field of leukemia, and this chromosomal anomaly remains as of now the only *specific* abnormality identified in any type of cancer. Nowell and Hungerford in 1960 described the finding of an unusually small acrocentric chromosome in peripheral blood and bone marrow of individuals with chronic granulocytic leukemia. The Ph^1 chromosome is a G-group autosome (chromosome 21 or 22) that has a deletion (or loss) of about one half to two thirds of its long arms (Fig. 12-1). The chromosome number usually remains diploid (46); the abnormality is found only in the hematopoietic cells and is not found in any other tissues of the body, such as skin or gonadal cells. The Ph^1 chromosome is present only in chronic granulocytic leukemia and not in any of the other myeloproliferative disorders like polycythemia vera or myeloid metaplasia, which at certain times may resemble chronic leukemia. Thus, the observation of the Ph^1 chromosome may be considered pathognomonic

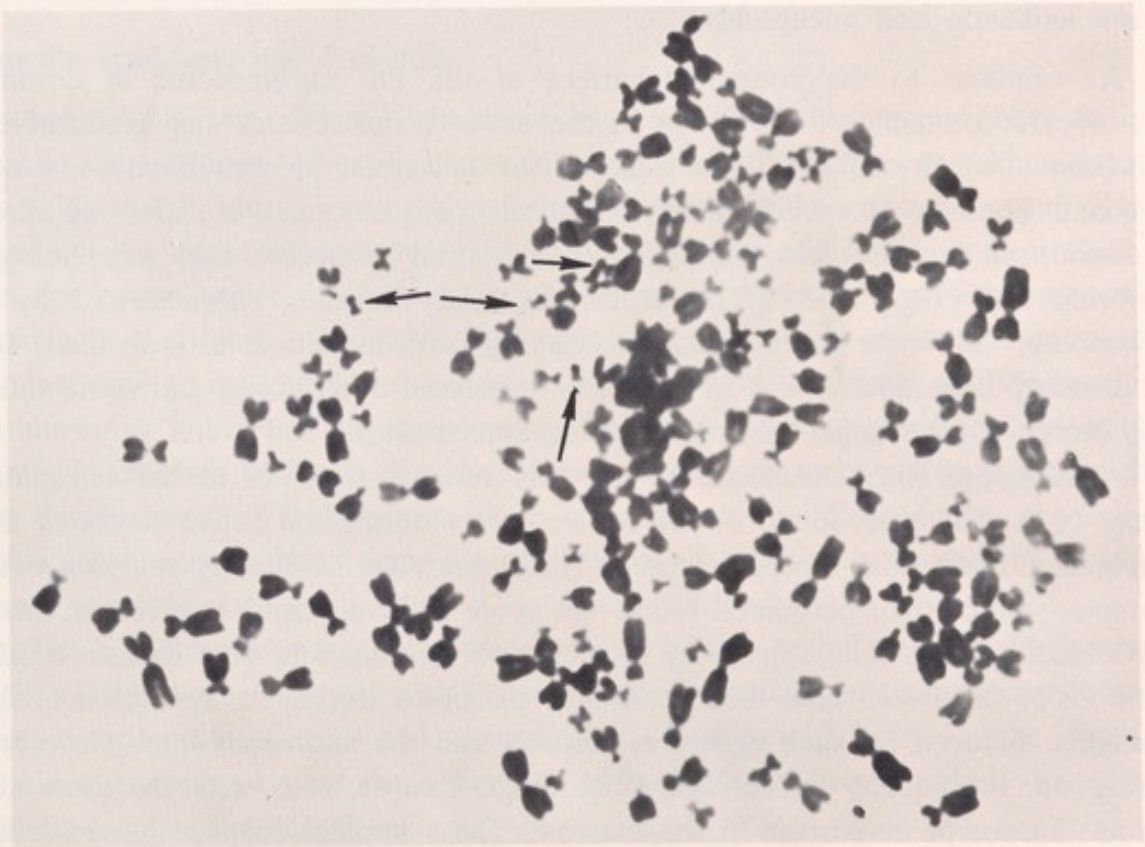

Fig. 12-2. Megakaryocyte with tetraploid chromosome number (184) and four Ph^1 chromosomes (arrows).

of the disease. Rare exceptions, including the infantile type of chronic leukemia, have been reported in which the Ph¹ chromosome is not found. However, these exceptions may represent variations of chronic leukemia.

The Ph¹ chromosome has not been observed in normal individuals, although it may be found in early stages of the leukemic process before the development of frank leukemic symptoms is evident. Evidence exists for the presence of the abnormal chromosome in all the hematopoietic cells (granulocytes, erythroid cells, and megakaryocytes, Fig. 12-2), so that it seems likely that the loss of genetic material from the 21 or 22 chromosome has taken place in an early hematopoietic precursor in the bone marrow.

After therapy (busulfan is the most effective drug for this type of leukemia), the Ph¹ cells may not be observed in the blood, but are *always* present in the bone marrow. Thus, the abnormality persists despite apparent clinical success of the chemotherapy.

The problem of whether this morphologic chromosome abnormality triggers off the neoplastic process in the blood cells, or whether the Ph¹ chromosome evolves secondary to the malignant change in the cells, remains speculative. Nevertheless, the Ph¹ chromosome disease is a *specific* and consistent diagnostic marker for the single type of leukemia. Since the chromosome anomaly may precede the actual signs and symptoms of leukemia, the search for the Ph¹ chromosome may be of great aid in early diagnosis of the disease.

Acute leukemia and aneuploidy

As opposed to the consistent pattern of the Ph¹ chromosome in chronic granulocytic leukemia, the findings in the acute lymphoblastic and granulocytic leukemias (which make up the bulk of the leukemias in childhood) are not constant. There is no specific abnormality, but there is instead a variety of chromosomal patterns involving aneuploidy (abnormal numbers) and morphologic abnormalities (Fig. 12-3). The acute leukemias are thus characterized by a "dysploidy," the type of abnormalities varying from individual to individual. Indeed, many individuals show no visible chromosome aberrations, and some show only morphologic changes without numerical abnormalities.

Aneuploidy, with chromosomal numbers ranging from 47 to the tetraploid range (92), has been found in the bone marrow during the active stages of the leukemic process, and during relapse. (The importance of directly studying bone marrow—rather than peripheral blood—in acute leukemia must be stressed, since the leukemic blast cells apparently do not replicate under in vivo culture conditions.) The aneuploid cells then apparently disappear during the remission of the leukemia, induced by such agents as steroids and the antimetabolites. However, during the subsequent clinical and hematologic relapse, cells with the same abnormal karyotype re-emerge in the marrow. These findings suggest that each individual's leukemic process has its own mutant chromosomal constitution, triggered by some previous disturbance during DNA synthesis or during the mitotic process.

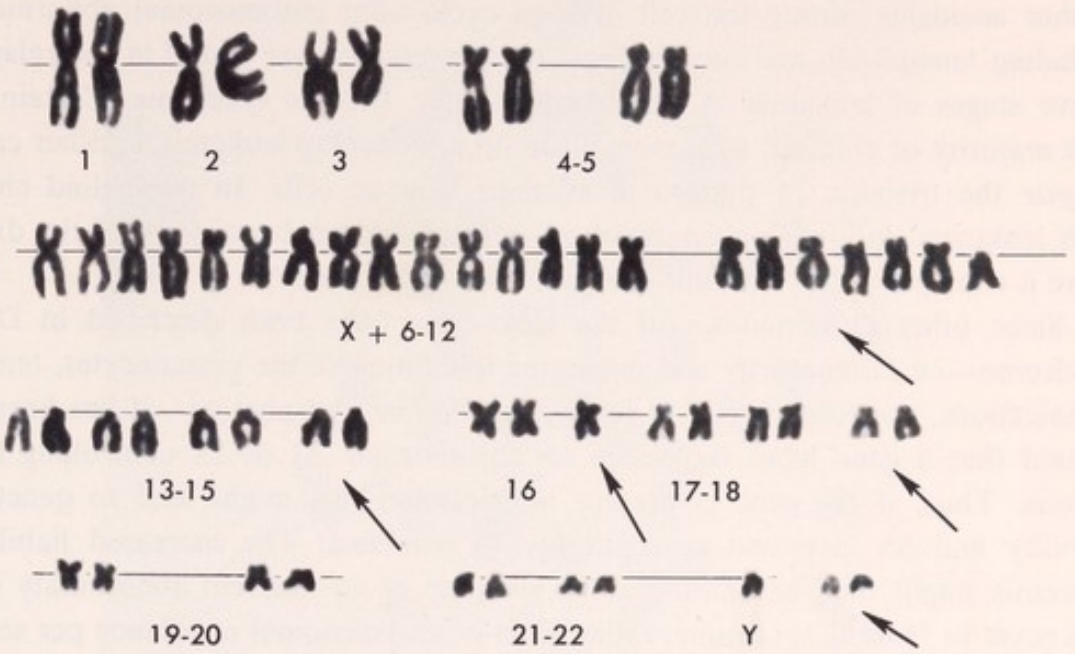

Fig. 12-3. Aneuploidy, an abnormal number of chromosomes, is found in the bone marrow of acute leukemia in relapse. The number of chromosomes in this leukemic marrow cell is 60. The supernumerary chromosomes are indicated by arrows.

Again, there is no final evidence as to which is the cart and which the horse—the chromosomal change or the neoplastic process.

Down's syndrome and leukemia

Individuals with Down's syndrome have a remarkable susceptibility to leukemia, the frequency of acute leukemia being from fifteen to twenty times greater in children with mongolism than in normal children in the same age group. Thus, although the expected occurrence of both mongolism and leukemia in a child in the age group under 4 would be in the range of one in ten million, the actual incidence of children with *both diseases* is obviously much greater. It seems reasonable now to assume that the aneuploidy of Down's syndrome and the resulting chromosome imbalance are somehow related to the striking predisposition to leukemia in children with this disorder. Thus, there seems to be strong evidence that the development of leukemia in these cases has been influenced by a common factor, the nondisjunction error during meiosis, that originally caused the chromosomal anomaly.

The significantly increased occurrence of children with Down's syndrome and their siblings with leukemia also indicates some parallel genetic predisposition to these disorders. Leukemias and mongolism are both more frequent in the offspring of older mothers, so that the incidences of both diseases are similarly associated with an increased maternal age.

Chromosomal imbalance may be a factor in the tendency of individuals with abnormal chromosome constitutions to develop leukemia. The trisomic mongoloid

cell, with its duplication of chromosomal material, may be unstable and prone to further accidents during the cell division cycle—but chromosomal abnormalities, including aneuploidy and morphologic rearrangements, are found in the relapse or active stages of leukemia in individuals without Down's syndrome. Certainly the vast majority of children with mongolism do not develop leukemia or other cancers *despite* the trisomic 21 pattern in all their somatic cells. In mongoloid children with leukemia, following chemotherapy and drug-induced remission of the disease, there is a return to the "normal" number of 47 chromosomes.

Since other abnormalities of the leukocytes have been described in Down's syndrome—i.e., immaturity and decreased lobulation of the granulocytes, tendency to infections, increased levels of leukocyte alkaline phosphatase—it has been postulated that a gene locus is present on chromosome 21 or 22 controlling leukopoiesis. Thus, if the gene is present in triplicate, this might lead to genetic instability and an increased susceptibility to leukemia. The increased liability to leukemia might then be considered as evidence of an inherent abnormality of the leukocyte in Down's syndrome, rather than of chromosomal imbalance per se.

Individuals with other chromosomal abnormalities are apparently also more susceptible to leukemia. Reports have associated Klinefelter's syndrome with leukemia, and there has been at least one case report of a D trisomy infant with congenital myeloblastic leukemia. The same predisposition to meiotic or mitotic errors may be involved as is speculated in Down's syndrome.

OTHER DISEASES WITH CHROMOSOME ABNORMALITIES AND INCREASED SUSCEPTIBILITY TO LEUKEMIA

Individuals with Fanconi's anemia (pancytopenia associated with multiple congenital malformations) have increased tendency to the development of leukemia. In 1966, several investigators found various types of chromosomal abnormalities on analysis of blood and bone marrow cells from children with this disease. Chromosome breaks, chromatid exchanges, structural rearrangements of chromosomal material, and evidences of abnormal cell replications were described (Fig. 12-4). Similar chromosomal abnormalities have been found in individuals with Bloom's disease (characterized by low birth weight, stunted growth, and telangiectatic erythematous skin lesions). Interestingly enough, these persons also have an increased incidence of leukemia.

Because of the previously described role of chromosomal abnormalities in leukemia, one might speculate about the relationships of those diseases in which there is an excessive number of chromosome aberrations to the ultimate development of leukemia in these individuals. The possibility exists that the breakages and chromosomal rearrangements indicate in such persons an increased susceptibility of somatic cells to be transformed and become malignant cells.

The association of genetically determined diseases such as Fanconi's anemia and Bloom's syndrome with both chromosomal abnormalities and leukemia constitutes evidence for the significance of hereditary factors in malignancy and en-

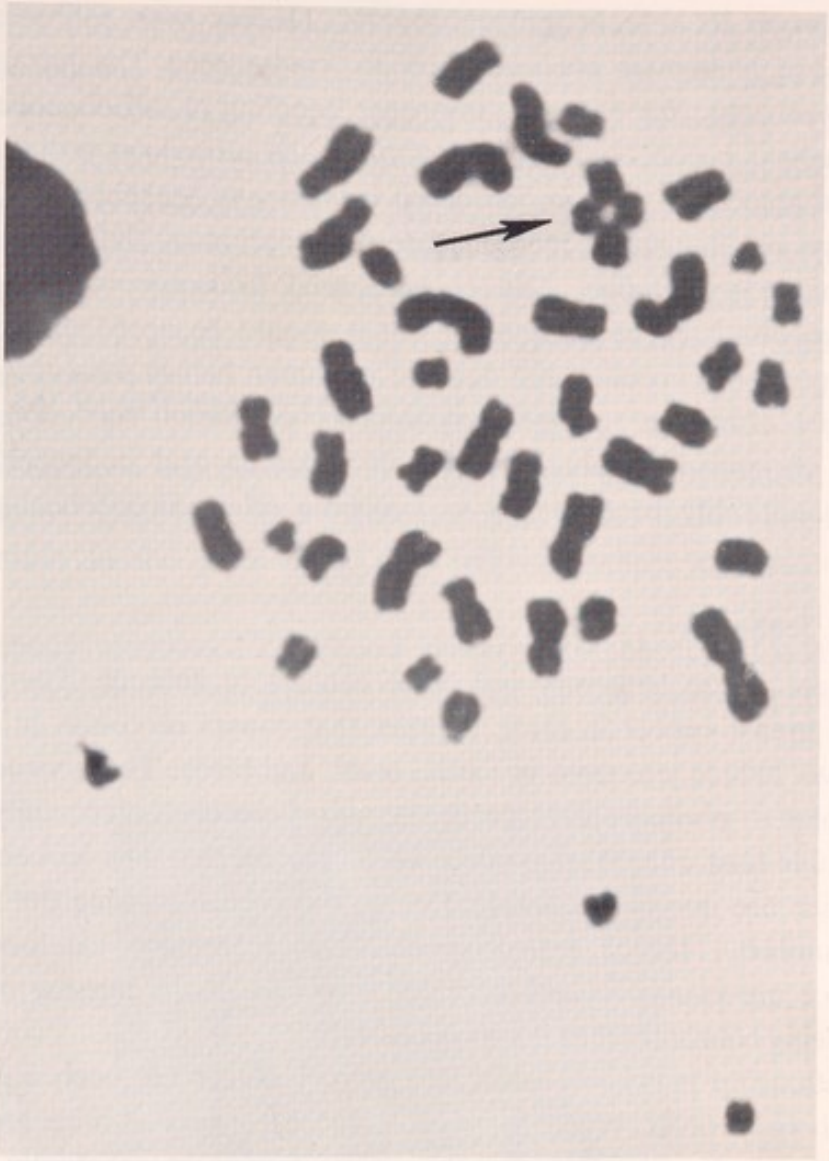

Fig. 12-4. Chromatid exchange formation, as shown by the arrow, is caused by breakage and then a reunion of the broken ends of different chromosomes. The phenomenon is noted in Fanconi's anemia and Bloom's syndrome.

couragement for research workers in leukemia to investigate these areas more closely.

Leukemia and irradiation

During the past two decades there has been a progressive increase in the incidence of leukemia, amounting to about 100% over that period of time. One of the factors that is blamed for the increase in the disease is irradiation, both background and medical.

Certainly it is now apparent that irradiation, at least in large doses, can cause leukemia. This has been documented by the studies of the survivors of the World War II atomic bomb explosions in Hiroshima and Nagasaki. Follow-up investigations of individuals who have been treated with irradiation for ankylosing spondy-

litis also point to its role in leukemogenesis. (It has been estimated that about 5% to 10% of leukemias are secondary to irradiation.) The hazards of irradiation are now obvious: for example, improper handling of radioisotopes, clinical exposure to medical x-rays, and long exposure to the ultraviolet radiation in sunlight have all been associated with an increased incidence of leukemia and cancers.

The actual mechanism of malignant transformation by the mediation of roentgen ray remains speculative. The chromosomal breakage induced by roentgen rays has been discussed in Chapter 5, but it should be noted that there are now numerous reports of chromosomal damage in human beings persisting from months to many years after one roentgen ray dose or accidental nuclear exposure. The evidence of chromosomal abnormalities in leukemia and in individuals with an apparent susceptibility or tendency to leukemia offers an interesting parallel for study.

Viruses and leukemia

Viruses can cause leukemia and other cancers in animals. There is one virus that induces breast cancer in mice, another that causes sarcomas in chickens; and several viruses induce leukemia in cattle, mice, and birds. These viruses have actually been isolated, photographed (with the aid of electron microscopy), and transferred from one host animal to another within the species. The leukemias in certain strains of mice are due to an inherited virus, the agents crossing the placenta prior to birth. Similarly, the so-called spontaneous mammary carcinomas in C3H strain of mice are caused by the neonatal infection of the nursing newborn mice, the viruses being transmitted in the mothers' milk.

The relationship between viruses and human cancer has been a problem much more difficult to unravel. While the virus-induced cancers of mice are examples of apparently genetically determined malignancies that were eventually proved to be maternally transmitted, thus far no evidence has been found of a similarly infectious pattern of transmission of leukemia in human beings. Spread of leukemia from parent to child (vertical transmission) or among unrelated individuals (horizontal transmission) has not been demonstrated in man. There have been only rare reports of the occurrence of leukemia in a child of a mother with leukemia during pregnancy, and, inversely, the rate of leukemia among mothers of leukemic children has not been higher than would be normally expected.

The Niles, Illinois, outbreak has been used as an example of the possible infection-like etiology of childhood leukemia. In this suburb of Chicago, there was a strikingly unusual number of cases of leukemia over a period of four years (1957-1960). In fact, seven of the eight affected children either attended the same parish parochial school or had siblings who did. Two cases of leukemia would have been expected from the national average during this time. This cluster of cases suggested a viruslike spread of the disease, and there have been several other similar clusters of leukemia reported in the last few years, such as in Orange, Texas, where three cases were diagnosed within one year.

Since there are thousands of communities the size of Orange, Texas, and Niles, Illinois, in the United States, one would expect many more cases of clusters of leukemia, if these outbreaks were indeed infectious in nature. On the other hand, statistically speaking, chance outbreaks might be expected even if the distribution of leukemia is random in the population. At any rate, even if viruses do play a part in the pathogenesis of leukemia, the process evidently must be very different from other virus infections. Certainly a long latent period between infection and onset of the disease might be hiding the infectious nature of leukemia in man.

HEREDITY OF SUSCEPTIBILITY TO CANCER

Genes conferring a susceptibility to a particular kind of cancer, involving a particular type of tissue and at a particular time, arise by mutation. Somehow, after transmission in the germ cells, they help to induce malignant changes in somatic cells.

The previously mentioned childhood cancer, retinoblastoma, was cited as an example of a hereditary malignancy. Although family genetic patterns suggest

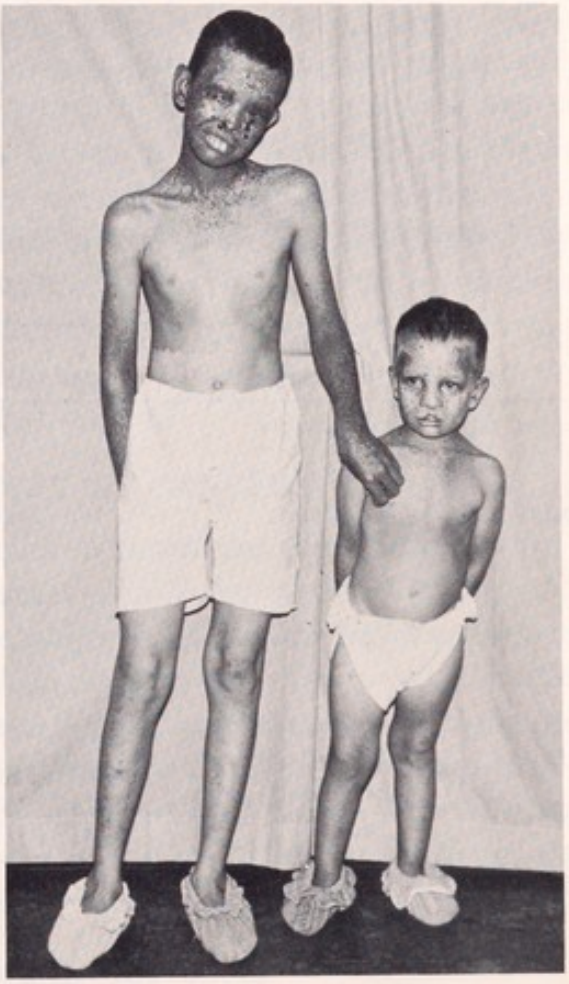

Fig. 12-5. Brothers, aged 6 and 11, who have developed squamous and basal cell carcinomas following xeroderma pigmentosum. The older child has since died. (Courtesy Dr. M. Fliegelman, Louisville, Ky.)

that it is inherited as a dominant trait, the occurrence of the disease in several children of apparently normal parents indicates possible variances in expression of the gene.

Although retinoblastoma is the only hereditary childhood cancer, several other examples of cancer with strong genetic contributions are known. The great majority of people with multiple polyposis of the colon will ultimately develop cancer. This disease is also due to a dominant gene and may be transmitted through many generations. Thus, a precancerous condition is inherited, one or more of the originally benign polyps—which are first observed in adolescence or early adulthood—eventually becoming malignant. Similarly, xeroderma pigmentosum, a benign skin condition, is inherited as a recessive gene. However, with exposure to sunlight, individuals with this disease show a striking tendency to develop skin carcinomas (Fig. 12-5).

Neurofibromatosis is characterized by multiple pigmented areas of skin and mucous membrane (café au lait spots) and by the development of many fibromas associated with peripheral or central nerves. These neurofibromatous areas frequently undergo sarcomatous change. This disease, which is inherited as a dominant trait, is frequently found in the individual with pheochromocytoma, a tumor of the adrenal gland. Although there is a small number of familial cases of pheochromocytoma, the genetic pattern in this disease remains unknown. The

Table 12-1. Inheritance of susceptibility to cancer—no apparent chromosomal abnormalities

Familial disease		*Genetic transmission*	*Mutation rate*	*Tissue of origin*
Multiple polyposis of colon	Cancer of colon	Dominant	1 × 10-5	Polyps of colon
Neurofibromatosis (von Recklinghausen's disease)	Neurosarcomas	Dominant	1 × 10-5	Peripheral or central nerves
Xeroderma pigmentosum	Basal cell cancer of skin	Recessive	—	Skin
Retinoblastoma	No preexisting disease	Autosomal-dominant with variable expression	1 × 10-5	Retinoblasts
Multiple osteochondromata (diaphyseal aclasis)	Osteosarcoma	Autosomal-dominant	—	Fibrous tissue of bone
Pheochromocytoma	No preexisting disease	Unknown	—	Chromatin cells of adrenal gland

relationship of neurofibromatosis and pheochromocytoma may be explained by the common embryologic origin of the chromatin tissue of the adrenal gland and of nerve tissue.

Another dominantly inherited precancerous disease is diaphyseal aclasis, associated multiple osteochondromas, generally arising when the affected individual is between 5 and 10 years of age. These tumors usually become sarcomatous in about 10% of the individuals affected.

In Table 12-1 are given the most common of the malignancies caused by cancer susceptibility genes. In retinoblastoma, there is apparently a direct transformation of originally benign tumors to frankly malignant tumors.

INHERITANCE OF OTHER CANCERS

Cancers that cause the deaths of one out of eight persons in the United States—cancers of breast, stomach, cervix, uterus, and rectum—have a much more complex genetic relationship. Indeed, although there are data to indicate that cancer does run in some families (especially malignancies of stomach, female breasts, and the colon), environmental factors may be as important as genetic factors in these families. Certainly, related persons have more similar environments than do unrelated persons.

Relatives of individuals with malignancies of stomach and breast have two to three times the expected incidence of cancer, although the incidence of cancers at other sites in these persons is the *same* as that found among other individuals in the population. There are similar findings for uterine and cervical cancers. There have been infrequent reports of "cancer families" with many members of the family having cancer at a particular site. However, the as yet unexplained decrease in the incidence of stomach cancer in the United States, for example, during recent years increases the possibility that environmental factors must play at least a considerable role in the etiology of this disease.

ROLE OF HEREDITY IN CANCER

The role of genetics in cancer has been shown to be (1) the inheritance of a susceptibility to a cancer or to a precancerous lesion, in rare cancers like retinoblastoma or multiple polyposis, dependent upon a single gene and transmitted by the classical Mendelian patterns and (2) possible intrinsic changes in somatic cells—either on a genetic point mutation or gross chromosomal basis—which may induce malignant transformation of originally normal cells. These intrinsic changes may be due to such environmental factors as irradiation or viruses, but more likely they may depend upon accumulation of various factors, including a genetic susceptibility to cancer.

COUNSELING CONSIDERATIONS

One of the most unpleasant diagnoses a physician has to reveal to parents is that their child has a malignancy. Under the best of conditions physicians view

the task as unpleasant, and under the worst of conditions, dreadful. In most cases it must be done as soon as possible.

When the diagnosis of a malignancy has genetic implications, the physician's burden is twice as troublesome. Parents voice concern for their other children or subsequent children, those children's offspring, and, if the event is likely, the offspring of the afflicted child. In this situation, the resources of the physician must extend beyond the knowledge of the disease and its consequences. The physician must call upon specific knowledge about that family and its resources.

The guidelines for counseling these parents cannot be as precisely defined as in some of the genetically related disorders. There is an elusiveness of the causal agent in some cases, and the questions of what and how many mutagenic factors enter into the disease process have yet to be answered. Consequently, the physician will be vague about answering some of the parents' questions. For this reason, honesty in answering questions that can be answered and honesty about professional ignorance are a must. Not only may the answers affect other family members and their offspring, but the lack of answers or the use of half-truths may give parents free rein to create their own answers. Half-counseling is psychologically worse than none at all. For example, unsophisticated parents may interpret vague statements about heredity and malignancy as their having the "mark of Cain." It does little good to give abstract statements about research studies, genes, chromosomes, mutations, and the like. These statements may help to support a belief that the family has "bad blood." The admonition for honesty, then, must be tempered by what the physician knows about the family. Too often one sees hard, objective facts given to parents not because the facts are appropriate but because they help the physician to avoid the human demands made on him as a counselor.

The admonition for honesty also applies to other people involved in helping the family. The clergyman's relation to the family should center on the same honest appraisal of the situation as does the physician's. As a vital help to the physician, he should avoid linking the disease with sin, and, especially, he should avoid giving well-meant qualifications of the diagnosis. Clergymen can be of most assistance when the genetic factors related to the malignancy are of such a nature that family planning is advised. In many families religion and the determination of the number of natural offspring are entwined. The physician cannot blithely advise parents to avoid having children, nor can he suggest that their children avoid having children, without considering religious views. In this situation the physician can seek advice from the family's clergyman or suggest that he, the family, and the clergyman discuss the matter together.

The physician, in turn, cannot abrogate his primary responsibility to the family by letting the clergy carry the counseling load. It is his counseling advice, based on medical knowledge, which must guide the family's actions.

Aside from giving medical advice, the physician, and especially the family doctor, can be helpful to the family in other ways. He can encourage and support the parents to maintain their normal living patterns for their children and for each

other. The stories about the crisis of sick or dying children pulling families together are legion; seldom told are the stories of similar crises tearing families asunder. Any illness in a child creates special privileges for the child and demands on the family. Too many times, unfortunately, the child with leukemia or some other malignancy is given so many special privileges that he is removed from normal family behavior and expectations. With the best of intentions, the parents have made him a pariah. The sick child who is no longer disciplined, who is given a Christmas tree in July, and catered to every moment can receive small comfort if such changes revolve around his illness. Other children in the family may also suffer from the distortions produced by these changes in the family's pattern of life. The physician, by judicious advice or by utilizing the resources of psychiatry, can try to help families avoid these dangers. Again, the family's clergyman may be a decided asset in helping the parents.

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Chapter 13

Mental retardation

Heredity has for some time played an important role in an explanation of mental retardation. After Mendel and Darwin helped to change many of our concepts about the transmission of traits suitable for environmental adaptation, heredity came into its own as a "cause" of the socially maladept. This approach led to many excesses, so much so that at the turn of the century all intellectual deficiencies were said to be inherited unless one could demonstrate some brain injury. Family studies were made of many cases of mental retardation. The lineages of such families as the Kallikaks, Jukes, and Nams were presented in great detail.

The Kallikak case, described by Goddard in 1912, has become the classic family study. Goddard hypothesized that feeblemindedness is inherited as a "unit character" according to Mendelian principles. He gave credence to his hypothesis by studying the ancestors of an 8-year-old retarded girl named Deborah. Goddard traced the family back to Martin Kallikak, a soldier in the American Revolution who had an illegitimate son by a feebleminded barmaid. Goddard traced two family lines from Martin Kallikak: one family line from the illegitimate son, Martin junior, and one family line from Kallikak's marriage to a normal woman. The marriage resulted in a family line of 496 descendents, all of whom were said to be intelligent, upstanding citizens. The descendents of the illegitimate son, however, consisted of 480 persons, of whom 143 were said to be retarded, 41 were sexually immoral, 3 were criminals, 3 were epileptics, 24 were alcoholics and 82 died in infancy. Only 46 of the descendents were said to be completely normal. Goddard used this evidence to indicate that feeblemindedness, a recessive factor, had been started by the barmaid. We now know, of course, that this case study, as well as others, while valuable at the time, had little scientific validity for supporting the conclusions drawn.

The evidence available now about the relation between heredity and mental retardation is less fraught with the scientific perils of the studies of Goddard and others. New knowledge has enabled us to isolate many conditions that involve mental retardation as a consequence of genetic abnormalities. As this knowledge has increased, we also have tended to attribute a smaller percentage of mental retardation to hereditary factors than we did in Goddard's time. Compared with

the high percentages (50% to 90%) cited in those times, the percentages cited now are in a more conservative range, from 15% to 25%. These new estimates represent the point of view that heredity should be ascribed only to those cases of mental retardation for which a genetic disorder has been isolated.

In other chapters in this book are described the genetic disorders that present concomitant mental retardation. These genetic disorders—such as Down's syndrome, Klinefelter's syndrome, PKU, Hurler's syndrome, and others—constitute our best cases for examining mental retardation and heredity. Yet, there are other instances of mental retardation in which genetics plays a more subtle and less isolable role. In this chapter, therefore, we will examine the more elusive relations existing between heredity and mental retardation. Also, in some greater detail, we will discuss further considerations for counseling families of the mentally retarded.

NATURE AND SCOPE OF MENTAL RETARDATION

The term "mental retardation" may be generally defined as subaverage or deficient intellectual functioning that is associated with impairments in learning and social adaptation. These deficiencies are usually attributed to cerebral deficits that have originated during prenatal life or infancy. It is recognized, however, that intellectual deficiencies can be acquired because of impoverished external conditions or because of disease processes and traumas occurring some time later in life. Acquired intellectual deficiencies will not concern us here, since mental retardation due to accidental cerebral traumas, infections of the central nervous system, or poisons is not likely to have a genetic component. A genetic component might be postulated for mental retardation due to malnutrition or cerebrovascular accidents, but such a component is not apparent enough to play a role in genetic counseling. Finally, as we have indicated, we are not primarily concerned in this chapter with known cerebral deficits related to genetic disorders. The retarded group that does concern us is the one said to display *familial* retardation. This group, which comprises about 80% to 90% of the mentally retarded population, presents a genetic problem yet to be solved.

From our working definition, mental retardation per se is not a disease entity but a concomitant set of symptoms that can be described in various ways. One point of view establishes mental retardation as a condition of subaverage intelligence that leads to inadequate educational achievement. The IQ is the major criterion used for evaluating these symptoms. From another point of view, mental retardation refers to social incompetence that leads to an individual's imprudent management of his own affairs. Laws and society's expectations are the criteria for evaluating these symptoms.

Whereas there is agreement that these viewpoints are related to mental retardation, there is some controversy about how much each of these viewpoints should be emphasized. For example, if we take an IQ score to evaluate mental retardation, we have to establish a particular score to separate the mentally retarded

from "normals." Should we pick a score of 75 or below as representing retarded intelligence, the person with an IQ of 76 (who is not called mentally retarded) would not seem especially more capable than the person with an IQ of 75. Yet, for a number of reasons, there has to be some such arbitrary use of a score. Some state laws, for example, use IQ scores to certify an individual for an institution for the retarded. If we take social incompetence to be our only guide for selecting the mentally retarded, we will tend to make different kinds of errors. Standards of social behavior are often arbitrary and vary greatly the farther one gets from the city. Also, overemphasis on social competency would tend to confuse mental illness with mental retardation, since emotionally disturbed patients also do poorly in society.

Recognizing the elusiveness of a hard definition of mental retardation, we will accept the premise that mental retardation can be described by two functional characteristics: an IQ below a certain score *and* social adaptiveness below a certain level of competency. These characteristics also show wide variation, ranging from extreme disability throughout life to an impairment so slight as to permit almost normal functioning in adult life. Table 13-1 shows IQ ranges and broad characteristics of the mentally retarded persons belonging to those ranges.

The number of mentally retarded persons in the United States is based on an estimate that about 3% of the population are so afflicted. In our present population of about 200 million people, about 6 million would be called mentally retarded. Also, it is estimated that more than 100,000 babies born each year are destined to become members of the mentally retarded population. By these estimates, the incidence of mental retardation is twice as high as the incidences of blindness, cerebral palsy, and rheumatic heart disease combined.

Among the retarded, the estimated incidence figures vary according to the degree of handicap. From Table 13-1 one can see that the most seriously affected individuals, the severely and profoundly retarded, make up a very small percentage of the total. These individuals, who need constant medical and nursing care, are likely to be found in public institutions. Most of the retarded population is made up of mildly and moderately retarded individuals who are less likely to be institutionalized. These individuals also constitute most of our population of familial retardates.

The number of living retarded adults, in or out of institutions, cannot be estimated directly from our incidence figures given in Table 13-1. The reason is that there is a distinctly higher-than-average death rate for retardates living in institutions, and it is likely that this excess mortality rate may be found for retardates living outside of an institution. Physical disabilities and serious medical problems are often allied with mental retardation in such a way that the more serious the retardation, the more likely it is that serious physical impairments will be found. These impairments often render the retardate susceptible to disease complications that can be fatal. Thus, for the persons most severely retarded we find a high mortality rate. Perhaps one out of five to one out of ten of these per-

Table 13-1. Degrees and classification of mental retardation

Degree of retardation	*Approximate percent of the retarded population*	*General characteristics*
Profound (IQ 0-19)	1.5%	Pronounced retardation; language abilities and social skills are minimal; completely dependent for care and supervision
Severe (IQ 20-35)	3.5%	Some training of self-help skills and language skills possible; adaptation to routines and useful habits possible, but supervision in a protected environment is necessary
Moderate (IQ 36-52)	6.0%	Generally considered trainable for language, social skills, and routine tasks; simple skills can be taught so that semiproductivity and semi-independence can be achieved in the community
Mild (IQ 53-69 or 75)	89.0%	Educable; through special education, academic and occupational skills can be acquired to a third to sixth grade level; self-support is possible

sons does not live to adulthood. Among the persons who are mildly to moderately retarded, excess mortality rates are still found, but these rates are only about one fourth of the rates for the more seriously handicapped. While it is no longer a truism that most mentally retarded individuals have a drastically truncated life-span, it is obvious that the conditions associated with mental retardation do modify the length of life for many.

GENETIC FACTORS

It would be convenient if mental retardation were always attributable to an isolable condition for which we have found a genetic or some other type of cause. The state of our present knowledge, however, does not permit us to attribute specific etiologies to those cases that constitute the majority of the mentally retarded. Most of them involve mild and moderate degrees of mental retardation and exihibit few or no physical stigmata, neurologic abnormalities, or other defects. They are aclinical except for one abnormality: subnormal intellectual functioning. Because their intelligence quotients fall below our arbitrary cutoff score of 75, they belong to a subpopulation of the mentally retarded not by diagnosis but by definition. This subpopulation, conspicuous by its lack of pathology, is said to have the familial type of retardation. In large part, to this group we ascribe limitations of intellectual ability because of limited genetic endowment.

To appreciate the relation between intelligence and genetic endowment, we need to accept the fact that variations in a population's gene pool influence known variations in some traits. On the strength of available evidence, the trait of intel-

lectual ability shows such a variation, and for this reason the genetic foundation for intelligence is assumed to be determined by polygenic inheritance. Like other traits related to polygenic inheritance, intelligence is assumed to represent the cumulative effects of many independent genetic determinants. Familial retardation, then, is related to polygenic inheritance because some retarded persons inherit (unknown) polygenic factors that govern their position in the lower levels of the continuous distribution of the trait intelligence.

The very nature of the polygenic model leads one to expect that mental retardation (as defined by IQ scores) in the population is found correlative with the degree of genotypic similarity. Thus, if we were to examine the relatives of known mentally retarded individuals, we would expect a higher incidence of mental retardation among them than in the general population. Also, we would expect that in some subpopulations that have a high incidence of mental retardation, the incidence of consanguinity would be higher. Both of these expectations have been fulfilled in several studies of mentally retarded individuals.

Although the rates of mental retardation have varied from study to study, the general findings are that among retarded individuals, 13% to 30% have at least one retarded sibling, 25% to 60% have at least one retarded parent, and 16% to 42% have at least one retarded child. In almost every study, the rates of mental retardation have been directly related to the percentage of genes expected to be held in common by the different family members. Grandparents and grandchildren of the retarded individual are least likely to be retarded; parents and siblings are most likely to be retarded. Studies on twins support these findings in that, of those identical twin sets with one retarded twin, mental retardation is found in 97% of the other members of the twin pairs.

The genetic determination of mental retardation receives additional support from evidence acquired on the relation between consanguinity rates and the incidence of mental retardation. Subpopulations constituting cultural isolates have been studied both before and after population mobility changed the consanguinity rates. For example, in a remote Swedish area the rate of mental retardation was approximately 20% prior to changes in the isolated people's mobility. After such changes, the rate of mental retardation was reduced to about 5%. In some cultural isolates studied, the rates of mental retardation have been so high that dominant rather than polygenic inheritance has been postulated. Consanguineous unions within families with a known history of mental retardation produce a markedly higher rate of familial retardation. For example, offspring from the union of first cousins have a rate of approximately 10% to 15%. As we would expect, of course, the incidence of consanguinity in cultural isolates and families also affects the rates of mental retardation due to specific genetic disorders such as amaurotic idiocy, gargoylism, and familial microcephaly.

The rate of familial retardation among offspring of familial retardates provides evidence for hereditary transmission and gives us some important risk figures for counseling. When both parents are retarded, approximately 55% to 60% of the

offspring will be retarded, 35% to 40% will have borderline or slow normal intelligence, and only about 4% will have average or better intelligence. When one parent is retarded and the other parent has borderline or slow normal intelligence, 35% of the offspring will be retarded, and only 10% will have average or better intelligence. It is obvious from these and comparable data that as the intelligence of one or both parents approaches the average, the proportion of offspring having retarded or inferior intelligence tends to decrease. If we compare these risk figures with the risks for having a retarded child by normal parents (about one half of one percent), then we see that the contemplation of reproduction among retardates or normals and retardates carries quite serious consequences.

The most difficult problem in applying these risk figures is that, for some individuals, mental retardation can be attributed primarily to poor cultural or environmental factors. The interaction between heredity and environment is too well documented to need exposition here, but it is important for us to point out that not all familial retardation is solely a problem of heredity.

Most families with the familial form of retardation tend to be in the lowest economic and social strata. Unfavorable social conditions and inadequate income are reflected in inadequate housing, poor nutrition, and poor medical attention—all of which can have a telling effect on the incidence of prematurity, infant mortality, and complications that result in defects of the central nervous system. Mild mental retardation is but one index of these handicapping conditions. Furthermore, the interpersonal integration of parents within many of these families may be distorted or even severed. In such families, the remaining parent is often too much concerned with economic realities to worry about the niceties of stimulating scholastic interests in the children. Even when the parent may be interested, there are too many children to care for to worry about intellectual stimulation. In part, these conditions may underlie the phenomena of defective verbal skills often observed in these children. Better accomplishment is found on those tasks requiring less parental intervention. Skills demanding manual dexterity and visual-motor coordination are often more adequate than verbal skills. As one would expect, mental retardation associated with these conditions is highlighted by poor reading and generally poor academic achievement. For this reason many mildly retarded children are not "diagnosed" until they enter school, where their disabilities are first detected.

The genetic counselor obviously should consider cultural and social factors present in those families presented to him. Such factors may offset his application of risk figures or the certainty with which he prognosticates a child's future. For example, when a couple wishes to adopt a baby born of parents living in the conditions described, the risks for that baby's being retarded are perhaps slightly higher than usual but not significantly so. It is only when other cases of mental retardation are known to exist among the immediate relatives of the parents that the risks become appreciable.

On the other hand, the genetic counselor should not be so swayed by the

presence of poor socioeconomic conditions that he is tempted to equate familial retardation with impoverished environments alone. Otherwise, he has the difficult task of explaining why most children in the lower socioeconomic classes are not mentally retarded, why some mildly retarded parents rear offspring of normal or even superior intelligence, and why some parents of high intelligence rear children with mild (as well as moderate, severe, and profound) retardation.

Definitive studies are yet to be made of the complex interplay between heredity and environment that results in mental retardation. What studies we have (and there are many) would support strong arguments that emphasize either heredity or environment. We have intended to present a strong genetic argument without implying that environment has no effect upon intellectual functioning. The genetic counselor's obligation is to impart what he knows about mental retardation as determined by genotypes under given environmental conditions. Until those conditions change (and we hope that social progress will produce such changes), our best evidence suggests that mental retardation tends to beget mental retardation.

COUNSELING CONSIDERATIONS

During the last twenty years profound changes have occurred in our ability to detect isolable causes of mental retardation. Bit by bit, medical science has eroded whole banks of ignorance that have stood solidly for hundreds of years. We now can treat some of the conditions associated with mental retardation; others, which remain untreatable, we understand well enough to give advice that might prevent their recurrence. For the cases in which both heredity and environment play a role, we can attempt (at least on paper) to engineer environmental changes that will give an individual the best possible chance to utilize his innate capabilities.

During this same period of time, many parents have become much better informed about mental retardation than their parents were. Parents' groups, national associations, and the public communication media have brought mental retardation within public view—if not within public focus. We need not now hide the child away, or discuss the mental retardation of a friend's or neighbor's child with the discretion reserved for indelicate subjects.

The trends that have begun in recent times have not necessarily made an immediate impact on all parents' understanding of familial retardation, however. Many parents with mildly retarded children have not been reached by the information publicly displayed about mental retardation, primarily because their retarded child does not "stand out." Unless he has some physical defect, he looks like their other children, and only his failures in school may bring him to medical attention. Many of the parents of these retarded children may not even consider school failures important, since the parents too had difficulties in school. Retarded children reared in a rural setting may not appear inadequate in any sense, because the environmental demands are not very complex.

For the foregoing reasons, and many others not mentioned, the majority of the

families in which familial retardation is prevalent will not voluntarily avail themselves of genetic counseling. If we see such families at all, it may be because someone in the school system has directed them to come to us. Most of the families that we do see, or that the family physician sees, are the families with more intelligent parents or more pressing social problems. Whatever the nature of the families who do and do not come to the physician's attention, there are some general considerations about mental retardation that are applicable to counseling all of them.

In a sense, families with mentally retarded children start to receive counseling when they first become aware, or are told, that their child is different. At that point they start asking questions and looking for answers. Families with severely retarded children, or families with children who have physical stigmata, may become concerned when the child is very young. Families with mildly retarded children, however, may not notice anything different until speech is expected to begin. Then, at least from more intelligent parents, the retarded child's lack of speech evokes concern and consequent trips to specialists.

In Chapter 3 we discussed the varied histories of families who have been from one professional to another before being counseled. Here we will not treat this subject in detail, except to reassert that the counselor or some member of the health team should ascertain what those histories have been. The family that has a child with "delayed" speech is likely to go to a clinic for hearing and speech disorders before getting to a clinic or person who will indicate the presence of mental retardation. Many times the family physician will promote such referrals. On other occasions, out of ignorance or misplaced kindness, the physician may not show concern at all; he may suggest that a child is a "late talker" who will "catch up."

Prior to formal counseling, the counselor must solve the problem of making a diagnosis. In the strict medical sense of the word, there is no diagnosis for most of the mentally retarded. All we know is that a child is mentally retarded because his intellectual development has been slower than other children of comparable ages. That fact alone may make many physicians uneasy, not only because many of them know little about the nature of normal intellectual development, but also because many physicians have little trust in the tests that assess such development.

The physician's lack of knowledge about psychometric tests and his lack of trust in test results often deter him from arriving at a diagnosis with the same comfort afforded by a well-known syndrome. Diagnosing Down's or similar syndromes has become commonplace among most physicians. Diagnostic certainty for such conditions is also reflected in the relative ease with which many physicians approach counseling parents with mongoloid children. But when the child's abnormal condition entails nothing more than intellectual retardation, squeamishness about diagnosis and counseling ensues. Many physicians, aware of the reservations held about the stability of the IQ (particularly among "deprived" children), will avoid making diagnostic statements. Others, who know that IQ measures improve in predictive validity with increasing age in the child, may suggest to parents that

no one can measure any child's intelligence with great accuracy until the child is 5, 6, or more years in age. In all such instances, parents are usually forced to fall back upon their own resources and their own judgment until the discrepancies between their child's and other children's development become obvious.

No one would advocate attaching a label of mental retardation to a child when there is *good* evidence that the home or social environment has not been conducive to normal development. Nor would one hastily use such a label when a child is hovering around the gray zone between mental retardation and normal intelligence. Caution in ascribing mild retardation to children below 1 year or 2 years of age should also be maintained. But, with these and other reservations, there is no justification for equivocating about mental retardation when our best evidence, from IQ scores, developmental histories, and parental observations, indicates that mental retardation is present.

An accurate diagnostic appraisal of mental retardation and the subsequent counseling of the retarded child's parents should, we believe, be carried out as soon as possible in the life of the child. If risks are involved for subsequent children, early diagnosis can have some effect on the parents' plans for governing the size of their family. The reproduction patterns of families with retarded children are likely to change as a result of genetic counseling. In one study, for example, reproduction rates dropped as much as 23% after chromosomal disorders had been diagnosed, 41% after autosomal recessive disorders had been diagnosed, and 2% after aclinical (familial) retardation had been diagnosed.

Even if it does not affect the parent's plans for family size, early diagnosis is especially important for helping parents to bring into play realistic expectations and management practices for the child. The sooner the parents find out that their child is retarded, and how seriously retarded he is, the easier it is for them to understand and promote the intellectual and emotional development that can be his. This is particularly important for the retarded child's development of an adequate image of himself as a person. Feelings of self-worth through accomplishment are as important to a mentally retarded child as they are to any other child. In some families, the parents' expectations of what their retarded child should be capable of doing may be based on what their other children have done or on what a normal child of the same age can do. If the retarded child has to measure up to discipline and learning standards that are too high, failure results; if such failure is experienced often, motivation flags. In other families, the expectations may be set too low and the child given no chance to learn to his potential. Such a child, said to be overprotected, may be more functionally retarded as an adult than one would expect from his IQ scores.

Whether or not the diagnosis is achieved early in the child's life, the diagnostic process should not give the appearance of being hasty. Even when the child is severely retarded and the diagnosis can be made at a glance, the parents should be made to feel that considerable time has been spent in achieving the diagnosis. This "window dressing" is not senseless. When the parents receive information carrying

such dire consequences, their belief in that information is often equated with the time and effort that physicians have spent in getting it. We have seen parents who have "shopped around" among physicians, not because they were looking for good news per se but because they could not believe that such bad news could be based on examinations lasting such a short time.

On the other hand, the diagnostic process should not be so drawn out that parents are kept in an anxious state of suspense for too long. This may happen when the parents are sent from one specialist to another. Sometimes a time-consuming series of referrals cannot be avoided because of the intricacies of the diagnostic questions. All too often, however, it is a professional form of passing the buck.

Once the physician has arrived at his diagnosis of mental retardation, by considering certain and uncertain genetic and nongenetic disease agents (as well as cultural agents), the physician should counsel *both* parents.

For practical reasons, the mother is often the only parent who receives information about a child from physicians. This, as well as the mother's role in the home, may account for the professional preoccupation with mothers of the retarded child. We must not forget, however, that the father is a parent too. The father, too, has to understand and accept the nature of the retarded child's handicap so that he, as well as the mother, can raise the child properly. If he gets his information secondhand from the mother, it is easy for vital information to become distorted or even omitted. It is also easy for him to deny the bad news related by the mother by indicating that obviously she must have misunderstood the physician. Further, counseling both parents can support the existing cohesion between the parents. In some cases, such counseling may reestablish cohesion between parents who have drifted apart because of the retarded child.

In counseling both parents, the physician should be prepared to give honest and factual information at the level of the parents' understanding. This obligation cannot be stressed too strongly. A physician can (and we hope, will) be sensitive to the parent's feelings and show sympathetic concern for their problem—but if he is not prepared to answer the parent's questions fully and frankly, all else fails. The parents' appreciation of their child's handicap is much more important than their appreciation of the physician as a warm and good person.

Diagnostic information per se constitutes but a small part of the total information to be imparted during counseling. If genetic risks are involved, obviously the physician should give such risks. Generally, however, most of the physician's counseling time will be spent on other subjects. The physician should be prepared to give to the parents an idea of their child's expected course of development, achievement in school, and independence as an adult. For example, the physician might indicate to the parents that their mildly retarded child can achieve a certain level of formal education and later take a gainful place in society. This can be spelled out in detail. Of course, with the more severe forms of mental retardation, the expectations for future achievements are lowered.

The usual questions about whether and when a retarded child will walk, talk, become toilet trained, go to school, and so on can often be answered validly if the physician is aware of the developmental course of children with varying degrees of retardation. We feel that the physician who counsels parents of the retarded should be familiar with such developmental standards; if he is not, he should have someone available *at that counseling session* who is. In similar fashion, the physician should be prepared to give prognostic information about physical development and physical anomalies. Parents will want to know about the child's expected course for such things as growth in height, development of teeth, and sexual development.

During counseling, it is important for the physician to emphasize the strengths as well as the weaknesses of the retarded child's abilities. At the same time that counseling can show what retarded children cannot do, counseling can stress what retarded children can do. The retarded child's future as an adult can look grim or even hopeless when the physician relentlessly explains the limitations imposed by mental retardation. For the mildly retarded child, at least, the physician can almost always talk about positive aspects, as well as restrictions, of the child's future.

The value of giving prognostic information in detail is that it helps to establish a continuous set of realistic goals by which the parents can pace their actions that promote the child's social and intellectual development. Parental actions that provide too much too soon or too little too late can have disastrous consequences for the retarded child and even for other siblings. A retarded child often gets more attention than any other child in a family. Some extra attention is rightfully given to young retarded children because of their susceptibility to illnesses and their prolonged period of dependency. If this attention is excessive, however, the other children may become quite jealous of their coddled and protected sibling. At the other extreme, in those families with unrealistically high social and intellectual expectations for the retarded child, failure is common. The other children may easily generalize from the retarded sibling's plight to what might be their own, should they not meet their parent's expectations.

The physician, through counseling, is not capable of anticipating all of the emotional stresses among members of a family with a retarded child. He can try, however, to help the parents set up appropriate guidelines for *everyone's* actions, so that the stresses are within realistic limits. Furthermore, the physician can encourage the parents to inform the other children about their retarded sibling's handicap, including the capabilities and limitations that such a handicap entails. In this way, the children may be able to establish their own limits so that they demand neither too much nor too little from the retarded child and themselves. In many families we have seen, the children are able to make continued adjustments with more success than the parents.

Finally, the physician should be prepared to help the parents arrive at tentative decisions regarding their and the retarded child's future. Genetic advice about

their having other children, suggestions and plans concerning adoption, and considerations for the retarded child's eventual placement in special schools or institutions represent broad topics that the physician should be prepared to talk about. In each case, he should be prepared to give specific information, rather than broad recommendations that would leave the parents informed but immobile. For example, if parents indicate a wish to adopt a child rather than run the risk of having another retarded child, the physician should be able to tell them about the laws governing adoption in their state and the kinds of agencies that provide services for adoption. In the same fashion, the parents' questions about special schools should be answered with the names of schools (if there are any available), rules for application, and the means by which parents can get their retarded child entered.

Of all the foregoing topics raised in counseling, institutionalization is the most difficult for physicians to discuss with parents. In the past and, unfortunately, in the present, attitudes about institutionalization have sometimes been dogmatic. Blanket recommendations about placing all retarded children in institutions or keeping all retarded children at home have been directed to parents without considering the child, the family, or the community.

The decision to institutionalize a retarded child is almost always made solely by the parents—yet, the process by which the parents arrive at that decision is not without outside influence. Information and opinions from neighbors, relatives, and the public communication media doubtlessly sway parental judgment. The physician should be aware of these influences, some of which may strongly interfere with the parents' own choice. More importantly, the physician should be aware that he too plays a persuasive role in the parents' decision-making process. He may think (and, in fact, is encouraged to think) that, during counseling, all he really does impart to the parents are the simple diagnostic and prognostic facts. It may be a comforting thought, but it is hardly realistic. The physician, by overt and covert means, often indicates what he thinks about institutionalization. For example, the fact that the physician does or does not broach the topic of institutionalization may convey to the parents some information about how reasonable he considers such a step to be. If the parents bring up the topic and the physician is evasive, uneasy, or seems to know nothing about institutions, the parents may feel that institutionalization is not advised. Such variations in counseling are numerous.

After he has evaluated the child, the home situation, and the community resources, it is the physician's responsibility to be prepared to open the topic of institutionalization and discuss its merits (or demerits) for the particular case. The evaluaton should not be cursory; it should include an appraisal of the economic, emotional, and intellectual assets of the parents, the needs of other children in the home, the need for long-term medical care (such as might be necessary for the severely or profoundly retarded), and the assets of the community vis-à-vis the institution.

A discussion with the parents about institutionalization should be given lots of time. On occasion, the discussion may run into several sessions. Sometimes, there may be direct or indirect involvement from other parties, such as clergymen, relatives, or other parents who also have retarded children. After such discussions, the decision itself does not have to be a hasty one. We have indicated to some parents that they should visit the institutions in question and come back for more discussion. The waiting lists of some institutions are so long that, after placing their request, parents still have a year or more to reconsider. Parents can be advised that no matter what move they make regarding their retarded child's placement in an institution, it is not irrevocable. Even after placement has occurred, the parents can, in light of changes in their family situation, take the child back into the home.

If the thought of institutionalization is entertained by the parents, the physician should encourage them to talk to their other children about such a step. Placing any child outside of the home, even for such a temporary thing as a short stay in the hospital, may evoke concern from siblings about their own security in the home. Sometimes, institutionalization of a child is explained solely on the basis of an illness that needs long-term care outside of the home. The other children may then respond to their own illnesses with the fear of being removed from the family In other families, children may believe that the retarded child has been removed because he was "bad" or did not act like other children. This, too, can be generalized to their own eventual fate when they misbehave or perform at an unacceptable level. The physician can help the parents to expect some of these reactions and, perhaps, even to circumvent them. We have found it useful to have older children present during the counseling session or to have parents interpret our findings to the children at their level of understanding.

Institutionalization is, of course, not the only recourse for giving the family respite from some of its burdens. Depending on the locale, day care centers, nursery programs, and even temporary residential placements are available. Local associations for parents of retarded children usually list all such public and private programs in the area.

As a final step, the physician should indicate to the parents that many civic agencies are available to help them. Almost every major city has at least one program for retarded children. In addition, most cities have parents' groups that provide their own supportive programs. Parents should be encouraged to join some such group, if for no other reason than the fact that they can get helpful advice from parents who have experiences and resources to share. When it comes to giving possible solutions to day-to-day problems, many of these parents' groups are much more helpful than "experts" in the field of mental retardation.

It would be difficult to anticipate all of the problems that may arise during counseling with parents of the retarded. Each family will bring its own special cluster of difficulties and will need its own special solutions. At times, the physician who takes on the responsibilities of counseling these parents may find his counseling resources strained. He may have to enlist the help of other agencies and

other professionals. But, in the main, if he is able to give honest, pertinent, and accurate information in an understanding manner to parents, the physician may be the first, and can be the best, counselor available anywhere.

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Chapter 14

Future perspectives in genetic counseling

In the foregoing chapters we have presented some of the information currently available about genetic disorders. We have also advanced some counseling approaches by which this information can be made useful to persons with questions about genetic disorders. In the present chapter we will offer some calculated guesses about what medical genetics will be like in the near future.

It is rather common knowledge, even to the average citizen, that the nature of medical care is changing in the United States. Advances in medical technology are responsible for eradicating or controlling most of the "old" serious diseases of childhood and some of those of adult life. With such advances, the types of diseases that we will redefine as serious—and the approach of medical practitioners who will treat these diseases—will likely be different in as little as ten years' time. Our "new" diseases, many of which are related to genetic disorders, certainly have been serious for some time, but their infrequency or their complicated etiology has kept them obscured and neglected.

Along with the changes in the incidence of "old" and "new" diseases, there has been a change in the concept of medical care. The interest of the public, as reflected in social programs and health legislation, is turning more to what the total quality of life can be than to how one can be kept alive longer under any circumstances. Declining death rates, per se, are no longer considered an adequate index of medical accomplishments. Health care is the new emphasis in medicine—and that includes, among other things, medical concern about family size, education, jobs, and the importance of helping children to grow up free from intellectual and physical disabilities. Chronic conditions, whether related to genetics, environment, or both, are our new health problems.

No medical student or practicing physician can view these changes without a sense of accomplishment and, at the same time, a feeling of being beleaguered. It is almost paradoxical that under the conditions in which death rates decline, the demands made on the physician are greater, and often more complex. Just contrast the medical school curricula of today with those of fifty years ago. In addition to the "basics" given then, one now sees lectures on mental retardation, be-

Table 14-1. Service facilities for genetic counseling

State	*City*	*Facility*
Alabama	Birmingham	University of Alabama Medical Center
Arizona	Tempe	Arizona State University
California	Berkeley	University of California
	Los Angeles	Children's Hospital
	Los Angeles	University of California School of Medicine
	Martinez	Genetics Consultation and Counseling Service
	Oakland	Children's Hospital Medical Center
	Palo Alto	Stanford University School of Medicine
	Palo Alto	Palo Alto Stanford Hospital
	San Bernadino	St. Bernadine Hospital
	San Bernadino	University of California Medical Center
Colorado	Denver	University of Colorado Medical Center
Connecticut	Hartford	Connecticut Twin Registry
	New Haven	Yale University School of Medicine
	Ridgefield	New England Institute for Medical Research
District of Columbia	Washington	Children's Hospital
	Washington	Georgetown University Hospital
	Washington	Howard University Hospital
Florida	Coconut Grove	University of Miami Child Development Center
Georgia	Atlanta	Georgia Marital Health Institute
	Augusta	Medical College of Georgia
Hawaii	Honolulu	University of Hawaii
Illinois	Chicago	Billings Hospital
	Chicago	Children's Memorial Hospital
	Chicago	Illinois State Psychiatric Institute
	Chicago	Medicine Blood Center
	Evanston	Evanston Hospital
	Springfield	Department of Public Health
Iowa	Iowa City	University of Iowa University Hospitals
Kansas	Kansas City	Kansas University Medical Center
Kentucky	Lexington	University of Kentucky Medical Center
	Louisville	University of Louisville School of Medicine
Louisiana	New Orleans	Tulane University Genetics Counseling Center
Maryland	Baltimore	Johns Hopkins University School of Medicine
	Baltimore	Sinai Hospital
	Bethesda	Children's Diagnostic and Study Branch, NICHD
	Bethesda	National Naval Medical Center
Massachusetts	Boston	Birth Defects Center
	Boston	Boston University Medical School
	Boston	Children's Hospital, Harvard Medical School
	Boston	Massachusetts General Hospital

Table 14-1. Service facilities for genetic counseling—cont'd

State	*City*	*Facility*
Michigan	Ann Arbor	University of Michigan Medical School
	Detroit	University of Detroit
	Detroit	Wayne State University School of Medicine
	East Lansing	Michigan State University
	Northville	Plymouth State Home and Training School
Minnesota	Minneapolis	Human Genetics Unit, State Board of Health
	Minneapolis	University of Minnesota Hospitals
Missouri	Columbia	University of Missouri Medical Center
	St. Louis	Children's Hospital
	St. Louis	St. Louis University, Glennon Memorial Hospital for Children
	St. Louis	Washington University Medical School
Nebraska	Omaha	Children's Memorial Hospital
	Omaha	Creighton University School of Medicine
New Hampshire	Hanover	Dartmouth College School of Medicine
New Jersey	Newark	New Jersey College of Medicine
New Mexico	Albuquerque	University of New Mexico School of Medicine
New York	Albany	Birth Defects Institute
	Buffalo	Buffalo General Hospital
	Buffalo	Roswell Park Memorial Institute
	Buffalo	State University of New York at Buffalo School of Medicine
	Jamaica	Creedmoor State Hospital
	New York	Albert Einstein College of Medicine, Yeshiva University
	New York	Columbia University College of Physicians and Surgeons
	New York	Cornell University Medical College
	New York	Mount Sinai Hospital
	New York	New York State Psychiatric Institute
	New York	Rockefeller University
North Carolina	Durham	Duke Medical Center
	Morgantown	Western Carolina Center
	Winston-Salem	Bowman Gray School of Medicine
Ohio	Cincinnati	Children's Hospital Research Foundation
	Cleveland	Cleveland Metropolitan General Hospital
	Cleveland	Cleveland Psychiatric Institute
	Columbus	University Hospital
	Dayton	Barney Children's Medical Center
Oklahoma	Tulsa	Children's Medical Center
Oregon	Eugene	Sacred Heart Hospital
	Portland	University of Oregon Medical School
	Salem	Fairview Hospital and Training Center
Pennsylvania	Philadelphia	Jefferson Medical College
	Philadelphia	St. Christopher's Hospital for Children
	Philadelphia	University of Pennsylvania School of Medicine Children's Hospital

Table 14-1. Service facilities for genetic counseling—cont'd

State	*City*	*Facility*
Rhode Island	Providence	Rhode Island Hospital
Tennessee	Knoxville	University of Tennessee Memorial Research Center and Hospital
	Nashville	Vanderbilt University Hospital
Texas	Austin	University of Texas, The Genetics Foundation
	Ft. Sam Houston	Brooke Army Medical Center
Utah	Logan	Utah State University
	Salt Lake City	Primary Children's Hospital
	Salt Lake City	University Medical Center
Vermont	Burlington	Mary Fletcher Hospital
Virginia	Charlottesville	University of Virginia School of Medicine
	Richmond	Medical College of Virginia
Washington	Seattle	Mason Clinic
	Seattle	University of Washington School of Medicine
West Virginia	Morgantown	West Virginia University Hospital
Wisconsin	Madison	University of Wisconsin Medical School

havioral psychology, school phobias, fetal medicine, chromosome disorders, organ transplantations, population control, and other specialized subjects. The number of medical specialists available to explore each of these topics has increased accordingly. As an index of the increasing specialization in clinical genetics alone, one need only examine the list (Table 14-1) of facilities now providing genetic information and remember that there were only a few genetic clinics about twenty-five to thirty years ago.

The following topics will give the physician a "feel" for medical genetics of tomorrow. He can even impart some of the knowledge about these topics to families who are short on hope for prevention and treatment of their genetic problems in subsequent children or in future generations.

EUGENICS

The problem of eugenics—the selective elimination of the undesirable genes and traits from the human race—at the present is a purely philosophic one, at least for the family physician. His personal involvement with eugenics begins only with his individual patients' questions concerning the desirability of marrying and of having children, and the likelihood of their children having certain congenital malformations and disorders. We do not consider it in the realm of this book to discuss in great detail the problems related to the perpetuation of genetically determined defects in society as a whole, but an understanding of eugenics is necessary.

Positive (or progressive) eugenics involves the inbreeding of good traits—practical with hogs or corn or such, but generally impractical in man. The sumo wrestlers of Japan did attempt positive eugenics of a sort by marrying the daughters of other wrestlers, but such planned attempts at the improvement of the species on a large scale have not been successful.

Negative (or preventive) eugenics involves improvement of the species by discouraging reproduction by those individuals who are "genetically undesirable." Despite the enthusiasm for the latter concept by Adolf Hitler and other historical personages, such efforts also seem doomed to failure because of the great difficulty in detecting the heterozygotes or carriers for mutant genes. This complication forces us to set a considerably lesser goal than perfection of human kind: that of counseling individuals and families so that they can avoid the often disastrous recurrence of genetic disorders and congenital malformations.

In the first chapter of this book we noted that in primitive societies defective children (and frequently the mothers, also) were killed. Certainly, even without the practice of infanticide, many of the individuals had abnormalities that were incompatible with life. Now, there has been a complete turnabout. Most of this book deals with the elaborate techniques developed to detect genetic defects and the therapeutic regimens that have been devised to preserve the lives of individuals with genetic disorders. Recognition of defects in the newborn (and now in utero) and effective dietary or surgical management are reversing the natural "selection" against these infants.

For example, probably close to 90% of the children who formerly died from retinoblastoma are now surviving because of advances in surgery and chemotherapy. Many of these children will be blind, but certainly able to reproduce. The same is true with phenylketonuria, galactosemia, diabetes mellitus, and a growing list of genetically determined or influenced disorders.

The bad genes seem to be on the increase in the population, but it does not necessarily follow that we are in imminent danger of being overwhelmed by the bad genes. Perhaps this is only a philosophical problem to the physician who is dealing with individual families, but it is a problem of magnitude to the population geneticists. At any rate, the mutation rate is so low in the human gamete (one mutation in 100,000 genes per generation) that we would seem to have no reason to fear that the normal population will soon be replaced by that of individuals with abnormal genetic factors.

More than ever the physician is faced with an increasing number of patients with genetic disorders. As the infectious diseases are eliminated, a greater percentage of his patients will have problems with a genetic etiology. He is also in a unique position to recognize genetic defects. In rare instances he can treat the affected individuals to limit the degree of mental and physical disabilities. In even more instances, he is in a position to help prevent recurrence of the disorder and perpetuation of mutant genes by giving eugenic advice.

FETAL MEDICINE

The genetic counselor can now give the parents of children with chromosomal or genetic disorders certain probabilities on recurrence of the disorders in their families. These odds offer no consolation at present to "high genetic risk" women who have accepted the odds, become pregnant, and have to wait out nine fearful months before their child is born. The antepartum detection of genetic defects may offer a new approach both in diagnosis and possible genetic manipulation of certain of these disorders.

Diagnosis: use of amniocentesis

Previously we discussed amniotic aspiration (amniocentesis) as a source of fetal cells for determination of sex. Presence of the sex chromatin body (Barr body) indicates a female. Its absence indicates a male. Prenatal determination of sex might have exciting implications in the family with a sex-linked disorder.

Congenital adrenal hyperplasia is associated with an overproduction of virilizing hormones by which the female infant is born with ambiguous, if not completely male-appearing, external genitalia. Standard treatment of the child with this disorder involves administration of cortisone to suppress the adrenal production of the abnormal hormone. When the physician is aware of a previous child with adrenal hyperplasia, he might utilize an amniotic tap. If the fetus is female, administration of cortisone to the mother presumably would suppress the fetal pituitary (and adrenal cortical output) and prevent occurrence of masculinization in utero.

There is some evidence that cretinism might be detected and treated during the prenatal period in a similar manner. Thyroid hormone has been given to mothers who had previously given birth to cretinous children and, thereby, were at risk for the recurrence of cretinism. The limited number of such studies do not allow us to draw any conclusions as yet. In fact, we are not able to evaluate the possible ill effects to the mother or to the unaffected child that may come from administering thyroid hormones during the prenatal period—yet, since therapy given during the postnatal period (prior to 6 months of age) does not always prevent damage to children with congenital hypothyroidism, the opportunities offered by prenatal therapy represent an exciting prospect in the field of fetal medicine.

Amniocentesis, followed by establishment of the amniotic cells in tissue culture, might also be of help in other "high genetic risk" pregnancies. For example, we might be able to avoid the problem of establishing odds or chances for the woman who has had one child with Down's syndrome or another chromosomal abnormality. Cytogenetic analysis of cell cultures derived from amniotic cell implants is now a well-established procedure. The amniotic cell karyotype would provide a "fail-safe" system for predicting the recurrence of a chromosomal error.

Techniques of in vitro culture of amnion cells (and of placental tissue, which is also fetal in origin) may in the future provide some assistance to the physician for detecting metabolic or biochemical disorders.

By this approach it may be possible to diagnose many of the hereditary disorders in utero. Galactosemia, which is caused by the hereditary deficiency in production of an enzyme, galactose-1-P-uridyl transferase, provides a case in point. Tissue cultures derived from skin biopsies from individuals with the defect demonstrate the metabolic defect in vitro. It is hoped that cell cultures of amnion cells or the placenta will also show the presence or absence of other enzyme defects, many of which are listed in Chapter 11.

Antepartum studies would be called for in the case of mothers with genetic high risks. These are mothers with previous children known to have chromosomal abnormalities or genetic defects. Such studies also could be applied to those parents with histories of exposure to roentgen rays or other teratogenic agents.

Prevention and treatment of abnormalities

Once an abnormal fetus is detected in the high-risk mother, we are still presented with the problem of doing something about it.

Although several states have allowed therapeutic abortion because of maternal rubella in the first trimester, no states allow the termination of pregnancy in other women with much greater risk of delivering a child with hereditary disorders or congenital malformation. At the present time, abortion because of high genetic risk is against the law in most, if not all, of the states. Therefore, the application of our diagnostic findings made during the prenatal period is limited. In addition, after the fourteenth or fifteenth week, therapeutic abortion presents a risk to the mother. Finally, of course, the chromosomal abnormalities and genetic errors that can be detected by the diagnostic techniques constitute only a small part of the total number of birth defects.

Another treatment possibility is to consider administering therapeutic regimens before the child is born. We have already mentioned the potential treatment of the female fetus with adrenal hyperplasia, which might prevent masculinization seen in the newborn. A successful treatment now being employed is that for erythroblastosis fetalis due to Rh incompatibility. In fact, erythroblastosis fetalis can now be used as an example of these techniques applied during the prenatal and perinatal periods. The techniques of postnatal exchange transfusions are now well known. Intrauterine transfusions are another step in this therapeutic application.

Transfusion of Rh-compatible blood cells can be accomplished by an amniotic tap, and repeated at intervals, so that, in effect, one has an exchange transfusion in utero. The affected infant may be born with almost all of his blood replaced by compatible red cells. This procedure has increased the number of viable infants who formerly were born with hydrops fetalis and usually did not survive. The use of an anti-Rh (D) gamma globulin, however, apparently will soon do away with the need for transfusions to be given at any time. There is good evidence that the administration of this gamma globulin to Rh-negative mothers during the immediate postpartum period will eliminate Rh sensitization in women.

Although transplantation is at an early stage, both in technique and in our understanding of basic mechanisms of immunology, one might at least speculate about future possibilities. For example, we can consider transplanting islet cell tissue into diabetics or livers into infants (or fetuses) affected with phenylketonuria. In the latter example, the transplanted liver would provide the missing phenylalanine hydroxylase enzyme. Kidney transplants could be considered for those children with renal rickets. Such organ transplantation might provide the ideal method for replacement of deficient enzymes or hormones.

Genetic manipulation in the future might involve the use of DNA and RNA materials to change certain traits in individuals. Drugs or chemical agents might be used to redirect the coded messages being sent from DNA to the messenger RNA. Also, we might utilize a biologic laser or partial cell irradiation technique to eliminate pinpoint genetic or chromosomal defects.

COUNSELING

These glances at future possibilities in human genetics for diagnosis, prevention, and treatment of hereditary disorders are remote to the physician. His concerns are in the present. His only tools and techniques are the ones available now to do the job for families of today. He has, however, one technique available now that offers unlimited help to his patients and their families. That tool—effective communication in counseling—should be considered as much a part of clinical genetics as any device or procedure mentioned in this book. The ability to interpret genetic risks, genetic facts, and other appropriate information to families is not an *additional* asset of the physician; it is an *essential* asset.

Genetic counseling in the past often stressed diagnoses and genetic risks. How one gave that information to families and how much one considered other, seemingly peripheral, aspects of genetic problems were individual preoccupations varying from physician to physician. Perhaps this is still true—but, as we have learned from the many families we have seen, our definition of genetic counseling should include more than giving facts about human genetics. Future definitions are likely to include more considerations about effective modes of communication between physician and families. We can only hope that medical schools will place some emphasis on this dynamic process in their curricula. The need for this emphasis in medical education is already there; the stories of our families tell us that it has been there for some time.

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Index